THE YEAR BOOK *of* MEDICINE

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Infections

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THE PRACTICAL MEDICINE YEAR BOOKS

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PART I

INFECTIONS

ANTIMICROBIAL THERAPY

Mode of Action of Penicillin Biochemical Basis for Mechanism of Action of Penicillin and for its Selective Toxicity is reported by James T Park and Jack L Strominger[1] (Univ of Pennsylvania) Uridine nucleotides have previously been reported to accumulate in Staphylococcus aureus inhibited by penicillin and the rate of accumulation indicated that if it were metabolized at this rate under normal conditions it must be used in one of the principal synthetic reactions of the cell However a structure analogous to part of the nucleotide is found in the cell wall of Staph aureus presumably a biosynthetic precursor of the bacterial cell wall

In the past several years more information on the nature of the bacterial cell wall has become available Alanine glutamic acid and lysine were highly concentrated in the walls of all gram positive organisms examined Other investigation has shown a peptide derived from spores of gram positive bacilli to be composed of alanine glutamic acid diaminopimelic acid and an unidentified amino sugar thought to be 3 O carboxyethyl hexosamine These data strongly suggest close similarity between structures of part of the cell wall and of part of the uridine nucleotide that accumulates in penicillin treated Staph aureus The amino sugar of the cell wall was identical to that of the nucleotide

The unique structures in the wall and the nucleotide suggest they may be metabolically related The striking similarity of structure and biologic experiments suggest that the uridine pyrophosphate N acetylamino sugar peptide is a biosynthetic precursor of the bacterial cell wall and that accumulation of this compound in penicillin treated Staph aureus results from interference by penicillin with the bio

(1) S en 125 99 101 J 18 1957

procaine penicillin 300 000 units and crystalline penicillin 100 000 units twice daily for 4 days irrespective of clinical progress Both groups received aspirin gargles at 6 hour intervals and all were treated in bed until temperature was normal for 24 hours

Of 121 consecutive patients satisfying the criteria and admitted to the trial 82 were subsequently found to have had Lancefield Group A streptococci on initial culture The most striking effect of penicillin on those from whom hemolytic streptococci were isolated was reduction in duration of pyrexia and leukocytosis by about 24 hours Duration of sore throat was only slightly shortened The small number of nonstreptococcic cases precludes definite statement but there was no difference in duration of pyrexia between those who received penicillin and those who did not This suggests that penicillin is unlikely to affect an acute sore throat unless streptococci are isolated

The importance of acute sore throat is in the risk of subsequent rheumatic fever or acute nephritis If typable group A streptococci are isolated risk of subsequent rheumatic fever is about 3% according to previous reports Experience in England in more than 300 soldiers of similar ages with endemic exudative tonsillitis from whom group A streptococci were grown suggests that the risk of an initial attack of rheumatic fever is less than 1% even without antibiotic treatment

It has been shown that rheumatic fever is not prevented unless hemolytic streptococcus is eradicated from the throat whatever the increase of streptococcus antibody in the serum Therefore if penicillin is used prophylactically against rheumatic fever a 4 day course is of doubtful value in view of the risk of inducing drug sensitivity

► [The lower incidence of rheumatic fever after streptococcic sore throat (less than 1% as contrasted with the figure of approximately 3% from the studies of Rammelkamp and others in the United States) may be due in part to differences in hosts or parasites or it may be a matter of the criteria on which a diagnosis of rheumatic fever is based In any event one wonders why the authors of the paper chose to employ a 4-day course when they acknowledge that the crux of therapy is prevention of rheumatic fever and also that a 10-day course of penicillin therapy seems necessary for that —Ed]

Penicillinase Producing Staphylococci Interfering with Penicillin Treatment in Scarlet Fever Hemolytic streptococci are invariably sensitive to penicillin but a proportion

synthesis of the cell wall The nature of the interference is unknown Possibly penicillin is a specific inhibitor of the transglycosidation reaction involving this uridine nucleo tide

The familiar effects of penicillin on morphology of bac teria—swelling filamentous forms large body formation production of penicillin insensitive L forms and lysis—are all explained by loss of integrity of the cell wall that follows interruption of cell wall synthesis Simultaneously with this work on Staph aureus other investigators have shown that Escherichia coli cells are quantitatively converted to proto plasts in the presence of penicillin and sucrose

The selective toxicity of penicillin is due to interference with a metabolic sequence not found in animal cells the bio synthesis of the cell wall It may be possible that competitive inhibitors related to the several unique components of the wall and nucleotide which would be useful as chemother apeutic agents might now be devised The availability of uridine nucleotide intermediates suggests that this possibil ity lies in the not too distant future

► [Park and Strominger provide here a most attractive clue to the mode of action of penicillin a problem surprisingly difficult to solve Espe cially intriguing is their suggestion in the last paragraph that this could open up a new approach to antimicrobial therapy —Ed]

Treatment of Acute Sore Throat with Penicillin Con trolled Trial in Young Soldiers W Brumfitt and J D H Slater in a controlled therapeutic trial gave penicillin to all patients with acute pyrexial sore throat without previous bacteriologic identification of the infecting organism The primary complaint was sore throat pyrexia was present admission was within 72 hours of onset of sore throat and there was no clinical evidence of more generalized disease

Patients signs and symptoms were assessed clinically ev ery morning on a special chart A swab from fauces and pharynx was obtained daily and white blood cell counts were made Patients were recalled 3-4 weeks after discharge ques tioned about recurrence of sore throat and about symptoms suggesting rheumatic fever or acute nephritis A throat swab and serum specimen were obtained and antistreptolysin ti ters determined

Patients receiving penicillin were given a combination of

( ) Lan t 1 8 11 Jan 5 1957

icol in 300 sporadic cases of typhoid fever—250 mg every 4-6 hours for 10 15 days beyond the day fever disappeared The relapse rate was 6% which compares favorably with other reported series of adequately treated patients and with the relapse rate before antibiotics were available Antibiotics apparently have no effect in reducing antibody levels The relapse phase may occur at a time when the antibody response is maximal

Probably the failure of antibiotic and antibody to affect the viability of the organisms is due to intracellular location of the organisms The cell wall appears to provide an effective barrier to the passage of chloramphenicol into the cell Reinvasion of the blood stream usually occurs at frequent intervals during the illness Often despite many days treatment with chloramphenicol viable forms may still be present in the blood

Any hypothesis regarding the effect of chloramphenicol on the relapse rate of typhoid fever must take into account that relapse occurs despite high antibody levels It is suggested that chloramphenicol promotes phagocytosis of viable organisms and that this creates a reservoir of tissue forms of the organism which is responsible for the high relapse rates in patients inadequately treated

► [It is now clearly evident that if high probability of relapse is to be avoided chloramphenicol treatment must be continued for many days after the fever has subsided.—Ed]

Novobiocin for Infections Due to Micrococcus Pyogenes William J Martin Fordyce R Heilman Donald R Nichols William F Wellman and Joseph E Geraci[5] (Mayo Clinic and Found) review accumulated data on novobiocin and report their clinical experiences For susceptible organisms the oral dose of novobiocin is as follows for infections of moderate severity 500 mg every 6 hours for adults for less serious infections every 8 or 12 hours for minor infections 250 mg every 6 or 8 hours for young children and infants 100 mg in a special capsule or syrup vehicle every 6 or 8 hours Given intravenously 500 mg at 12 hour intervals and intramuscularly 250 mg every 6-8 hours novobiocin has had no adverse effect

A total of 53 patients with micrococcic infections were treated Of 7 with micrococcic bacteremia sterilization of

(5) J A M A 162 1150 1153 Nov 17 1956

of streptococcic infections fail to respond promptly to penicillin treatment The clinical result may be good with disappearance of local symptoms and fall of temperature but bacteriologically the patient remains in the streptococcus carrier state In scarlet fever and streptococcic tonsillitis these failures are generally ascribed to circumstances interfering with the diffusion of penicillin to all sites of the bacteria as in large lymphadenitides or pronounced hyperplasia of the tonsil

Gosta Tunevall[3] (Infectious Diseases Hosp Stockholm) examined a number of such resistant patients in 1954 and found a significant number with penicillinase producing pyogenic staphylococci Their presence in the nose or throat cultures seemed to be the predominant factor in the poor bacteriologic result with penicillin therapy Of 14 patients who responded poorly and in whom resistant staphylococci were present 10 had lymphadenitis and/or tonsillar hyperplasia

Since penicillin resistant staphylococci in man produce penicillinase the most likely explanation of the observed facts is inactivation of penicillin in the site of infection Lymphadenitis and tonsillar hyperplasia are likely to afford good conditions for this process

In the discussion H Ericsson reported similar findings in patients treated for beta streptococci infection of burns When penicillin was used routinely for some time in these patients at least 75% were also infected with penicillin resistant Staphylococcus aureus

► [This is an interesting idea which may well bear on the varying rate at which streptococci disappear from the throats of different people during penicillin therapy —Ed]

Relapse State in Typhoid Fever Treated with Chloramphenicol The incidence of relapse in typhoid fever treated with chloramphenicol depends on the length of therapy and not on the actual dosage used Large loading doses do not reduce the relapse rate Courses of therapy of less than 7 days usually have a high relapse rate i e 12 25% The failure of chloramphenicol in this disease to reduce the incidence of relapse incidence of complications and carrier rate has been disappointing

Kenneth C Watson[4] (Univ of Natal) used chloramphen

(3) A ta path et m c b L sca d v s pp 111 pp 127 129 1956
(4) Am. J T p Med. 6 72 80 J uary 1957

strain in the lesion and implantation of a new strain during treatment

Novobiocin frequently failed to eradicate offending organisms from infections caused by other gram positive cocci such as Diplococcus pneumoniae Streptococcus pyogenes and enterococcus

Some Laboratory and Clinical Experiences with New Antibiotic Vancomycin which is obtained from Streptomyces orientalis are described by Joseph E Geraci Fordyce R Heilman Donald R Nichols William E Wellman and Griff T Ross [7] Vancomycin is predominantly bactericidal and active primarily against gram positive bacteria particularly staphylococci It shows no cross resistance with other antibiotics is of relatively low toxicity and stimulates only slow and slight resistance by the staphylococci

After oral administration little or no vancomycin was found in the blood and only small amounts were detected in the urine After a single intravenous injection however adequate levels persisted in the blood serum for 24 hours and large quantities were excreted in the urine Intravenous treatment was given to 9 patients in 500 mg doses every 6 hours for as long as 3 weeks With either oral or intravenous vancomycin the feces became odorless or nearly so strains of clostridium disappeared and Streptococcus faecalis organisms disappeared or were reduced in number Gram negative flora persisted

The only signs of toxicity were an occasional chill dermatitis in some and minimal to severe localized phlebitis The chill appeared with earlier batches of vancomycin and occurred in 6 of 94 persons In 4 a macular morbilliform eruption developed over the arms and thorax Minimal to severe phlebitis occurred after multiple intravenous injections

Vancomycin must be given parenterally except for the treatment of staphylococcic ileocolitis Preliminary clinical experience indicates promise in the treatment of staphylococcic infections Because of its bactericidal effect and the large quantities excreted in the stool after oral administration it would appear to be the antibiotic of choice in therapy of staphylococcic ileocolitis Preliminary results justify fur

(7) P St ff M t M y Cl 31 564 582 O t 12 1956

the blood in 5 coincided with novobiocin treatment In 22 cases of skeletal and soft tissue infections the clinical result was satisfactory in 20 In 13 patients with micrococcic enterocolitis the flora of the stools reverted to normal after novobiocin in 24 72 hours clinical improvement was evident Of the total clinical results were satisfactory in 48 and appeared equivalent to those expected with other available antibiotics

The most frequent untoward reaction was allergic dermatitis No patient developed kidney or hemopoietic damage Estimated frequency of skin rash during treatment was 9% In 2 patients the M pyogenes isolated after a period of treatment with novobiocin required a greater concentration of the antibiotic to inhibit growth than did the organism isolated before treatment

Novobiocin may prove especially useful in treatment of micrococcic infections that are resistant to other antibiotics The allergic dermatitis indicates need for special care in distribution of the drug Clinical experience with novobiocin in micrococcic infections is thus far encouraging

► [This drug best known by its trade name—Albamycin®—undoubtedly has a place in treatment of staphylococcic infections A bad feature is the high incidence of allergic dermatitis and other untoward reactions (see following report) —Ed]

Clinical and Bacteriologic Evaluation of Novobiocin in 75 Patients is reported by Joyce Z Pearson Alvin Somberg Ira Rosenthal Mark H Lepper George Gee Jackson and Harry F Dowling[6] (Univ of Illinois) Of 20 with pneumococcic pneumonia poor results were observed in 2 Four of 5 patients with streptococcic pharyngitis showed a good clinical response but streptococci could be cultured from 4 patients on the 3d 6th 9th and 12th day of therapy Of the 75 patients treated 14 (18 7%) had untoward reactions of leukopenia hematuria arthralgia or eosinophilia

The clinical and bacteriologic response of patients with staphylococcic infections to novobiocin supports the laboratory evidence and indicates that this drug suppresses staphylococcic growth In 6 patients staphylococci persisted in 8 of 25 specimens cultured for bacteria near the end of treatment The bacteriologic failure was due to development of a strain resistant to novobiocin persistence of a sensitive

(6) A M A Arch I t M d 98 273 31 Septembe 1956

antagonistic to bacteriostatic drugs This has been con firmed for penicillin but not for streptomycin The discrep ancy is partly due to the arbitrary time of incubation—24 hours After 8 hours there is an antagonism between strep tomycin and a bacteriostatic drug which on further incu bation disappears and is replaced by synergism

The usual method of testing the inhibitory sensitivity of organisms isolated from patients with bacterial endocardi tis can no longer be accepted as a guide

► [The method of sensitivity testing which is described is a practical one for ordinary use and has the additional advantage of providing informa tion on synergism antagonism and bacteriostatic and bactericidal effect —Ed]

Absorption and Excretion of Sulfamethoxypyridazine New Long Acting Antibacterial Sulfonamide Sulfameth oxypyridazine (3 sulfanilamido 6 methoxypyridazine) is a new antibacterial sulfonamide highly soluble in urine and well absorbed from the gastrointestinal tract with good penetration into cerebrospinal fluid and prolonged action Men given a single dose of 4 Gm absorbed it well and main tained high levels for long periods Since antibacterial activ ity of sulfamethoxypyridazine weight for weight is similar to that of sulfadiazine and since plasma levels of 10 mg /100 ml are optimal such levels can be approximated with 1 Gm every other day On this dose no untoward effects were noted but single doses of 3-4 Gm usually caused headache Altered fluid intake did not influence the level of the drug in plasma or rate of excretion in urine

According to Roger L. Nichols and Maxwell Finland[9] (Harvard Med School) if untoward effects do not develop during prolonged use of the drug sulfamethoxypyridazine should be valuable in continuous prophylaxis of strepto coccic infections and recurrent rheumatic fever and perhaps in prevention or suppression of other subacute or chronic bacterial infections for which sulfonamides have proved use ful In single doses of 1 Gm it may be ideal for prophylaxis or eradication of meningococcic infections and carriers from members of families or communities particularly in schools military installations etc Trials of this agent may also be warranted in suppression or prevention of relapses of chronic urinary tract infections particularly after they have

(9) J L b & Cl Med 49 410 4 1 M b 1957

ther use of this antibiotic particularly for serious staphylo coccic infections

► [Vancomycin seems to be a potent bactericidal agent but the necessity for intravenous administration and the side reactions mentioned here seem to indicate that it will have a somewhat limited place in clinical practice —Ed]

Action of Six Antibiotics Singly and in Combination on Enterococci Isolated from Cases of Subacute Bacterial Endocarditis was studied by T R E Pilkington S D Elek and Pamela Jewell[8] (London) To cure subacute endocarditis bactericidal action is required Inhibition of growth is not sufficient A full laboratory investigation of organisms isolated from patients should include both inhibitory concentrations and bactericidal effect of antibiotics alone and in combination Bactericidal action was tested by transferring the organisms from the surface of one agar plate containing antibiotic (the primary plate) to the surface of a second plate free of drug

Penicillin and streptomycin were found to be bactericidal at levels not much greater than the inhibitory concentrations while chloramphenicol chlortetracycline and oxytetracycline failed to kill in concentrations many times greater than their inhibitory levels Bacitracin was bactericidal in the higher concentrations tested This explains why the routine test based on inhibitory effect is useful for assessing penicillin and streptomycin but misleading for chlortetracycline and oxytetracycline

Subacute bacterial endocarditis presents special problems to both clinician and bacteriologist The organism must be killed by the antibiotic not just inhibited Blood concentrations greater than the minimum bactericidal level are needed to enable the drug to diffuse into the lesions and provide local bactericidal activity Therefore the choice of antibiotic is much more limited than in most other infections The customary laboratory test for antibiotic sensitivity is inadequate For the newer antibiotics the bactericidal and bacteriostatic levels are often far apart and the choice of an antibiotic based on the inhibitory test may lead to clinical failure

The clinical significance of antagonism is not established Previous reports have claimed that bactericidal drugs are

(8) J Lab & Cl Med 47 56 572 April 1956

sponse to prednisone was so prompt and impressive that even without controls it seems clear that the drug had a favorable effect on the hemolytic process This is consistent with the action of cortisone in other acquired hemolytic anemias Use of prednisone or cortisone in management of blackwater fever is therefore recommended

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STAPHYLOCOCCIC INFECTIONS ACQUIRED IN HOSPITALS

Clinical Staphylococcic Infections—Staphylococcic Infections Currently Encountered in Large Municipal Hospital Some Problems in Evaluating Antimicrobial Therapy in Such Infections Maxwell Finland and Wilfred F Jones Jr[3] (Harvard Med School) made a spot survey of all the wards of the Boston City Hospital during the latter part of January 1956 noting in each patient whether a staphylococcic infection of any type was present whether it was present when the patient was admitted and whether any antimicrobial therapy had been given immediately before or after its clinical appearance or recognition

Of the 1 172 patients in the hospital 181 had some type of staphylococcic infection Of these 113 (62%) apparently acquired the infection after hospitalization Sixteen had severe infections including 6 with pneumonia and empyema 3 with secondary infections of wounds and burns 1 with postcraniotomy meningitis 1 with infected venous cut down associated with prolonged bacteremia 2 with extensive carbuncles and infections of soft tissue 1 with subdiaphragmatic abscess occurring after a clean laparotomy and 2 with staphylococcic bacteremia of undetermined source

Ninety seven patients had less severe infections which caused prolonged morbidity including 52 with secondary infections of primarily clean surgical wounds burns or ulcerations (particularly decubitus ulcers in severely ill patients or those with severe injuries or fractures) 39 with multiple furuncles or abscesses of various sizes 5 with pulmonary infections and 1 with a urinary tract infection following instrumentation

Among the house staff 18 had large furuncles or carbun

(3) A N w Y k A ad Sc 63 (rt. 3) 191 05 1956.

already been actively treated and cured or suppressed with the same or other effective agents

► [Unless some serious toxic effect is subsequently discovered this drug marketed under the trade name Kynex® appears to have a bright future Administration of 1 Gm every 48 hours would b practicable for long term prophylaxis or suppression of such processes as stubborn urinary infections —Ed]

STEROID THERAPY IN INFECTION

Treatment of Mumps Orchitis with Corticotropin and Cortisone Erkki Klemola and Pekka Somer[1] report results in 105 patients Corticotropin was given to 41 cortisone to 11 and a placebo to 53 The dosage of corticotropin was 40 I U the 1st day 20 the 2d and 3d days and 10 units of long acting corticotropin Cortrophin Z (Organon) the 4th day The dosage of cortisone was 100 mg twice daily the 1st and 2d days 150 mg the 3d day 100 75 50 and 25 mg the 4th 5th 6th and 7th days respectively using Cortone® (Merck) intramuscularly

No significant difference was observed in the treatments regarding duration of fever and symptoms In each group treated there were patients in whom fever increased and swelling was aggravated even several days after institution of treatment However there were some in all groups in whom symptoms subsided immediately with therapy

► [These results are impressive because of the large number of cases treated and because of the control observations However Petersdorf and Bennett (A M A Arch Int Med. 99 222 1957) came to the conclusion that steroids given in larger doses i e 300 mg cortisone orally as an initial dose then 200 mg /day were definitely beneficial in mumps orchitis —Ed.]

Treatment of Blackwater Fever with Prednisone The exact cause and mechanism of blackwater fever is still obscure but it should be regarded as an acute acquired hemolytic anemia occurring only in patients who have had malaria H C Trowell and J M Vaizey treated 5 patients with prednisone Because this condition is now rare control studies were not possible However results appeared sufficiently satisfactory prompt and consistent to justify presentation In each patient diagnosis was established by methemalbumin in the serum detected spectroscopically Re

(1) Nord med 56 1159 1129 Aug 9 1956
(2) Lancet 1 81 128 Dec 2 1956

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(1) A n. New Y k A d. S 65 (art 3) 191 205 1956.

cles Of 7 nurses absent from duty because of staphylococcic infections 5 were hospitalized because of the infections 9 others had had recent treatment for staphylococcic skin infections At least 8 ward attendants had significant infections of the exposed skin surfaces

► [The data provided by the spot survey of one hospital are both astonishing and frightening Doubtless the danger exists in nearly all of our hospitals (see next abstract) —Ed.]

Some Aspects of Hospital Infection H Rocke Robertson J C Colbeck and W H Sutherland[4] (Vancouver B C) report difficulties and extent of contamination in the hospitals with which they are associated

In 6 years there have been a variety of infections in all types of patients young and old The commonest site is the skin with resulting boils on any part of the body surface most frequently the backs of patients confined to bed Wound infection is the next most common It occasionally develops early as an acute massive infection but more often on the 8th or 9th postoperative day producing a slow grumbling indolent type reaction

Staphylococcic pneumonia is more common than in the past It is present in some patients on admission and develops in others during hospitalization It is alarming to see staphylococcic pneumonia develop as a complication (sometimes fatal) in patients whose primary disease is not ordinarily fatal

How can this organism so easily killed by moderate heat and by many antiseptics create such havoc in a hospital that appears spotlessly clean? The staphylococcus can survive and maintain its virulence for a long time in dry fine dust which has extraordinary powers of movement and penetration This was demonstrated when 2 patients with open staphylococcic lesions were allowed to live and move about in a sterilized room Within 1 2 days the beds floors walls chairs tables bath toilet seat wash basin door handles mattresses sheets blankets pillows and pajamas were grossly contaminated with staphylococci

To correct contamination in a hospital the organism must be constantly attacked on all fronts Even one small reservoir may permit widespread contamination Blankets mat

(4) Am J S g 92 233 239 August 1956.

tresses and the like are the most important reservoir of infection Sterile sheets do not prevent migration of organ isms from the mattress and blankets Handling of dirty linen must be reviewed perhaps dry dusting dry sweeping and floor polishing abandoned in the wards and washing facil ties for both physicians and patients and operating theater technic improved

Series of Postoperative Infections Nosocomial infections seem to have become a far greater problem in the era of chemotherapeutics than before Most reports of postopera tive infections have not definitely established their source David Sompolinsky Zyskind Hermann Per Oeding and Joan E Rippon by a special series of investigations dem onstrated that more than 80% of all infections had a common source and wound infections could be almost entirely pre vented by simple means

The etiologic agent in each case was a coagulase positive strain of Staphylococcus aureus Frequency of wound in fections increased steadily until in January 1954 36% of pa tients with operations developed infections some with se rious complications such as empyema and subcutaneous and intermuscular abscesses Most infections occurred after ma jor chest surgery with long exposure of tissue

No serious flaws could be detected in handling of sterile materials or in sterilizing equipment Most doctors and nurses carried Staph aureus in the nasopharynxes Air bac teria were examined by settle plates and calculations showed that during a 2 hour operation over a sterile field of 3-4 sq m a minimum of 60 000 bacteria settled on the field About 95% were white coagulase negative staphylococci with only 1 2 colonies that were coagulase positive

Of 27 staphylococcus strains isolated from 19 different cases 6 strains were of four different types The other 21 strains were identical in group III Patterns of lysis agglu tinability and sensitivity were studied in the carriers Char acteristics of the bacteria isolated narrowed the possibilities to 5 carriers and further tests by antibiogram and reaction to phages implicated 2 persons a male and a female nurse both working in the operating suite When they were given a 6-week holiday 35 operations performed during this pe

(5) J I Sect. D s. 100 1 11 Jan Feb 1957

riod were infection free When they returned to their usual duties 3 new cases of postoperative infection occurred 2 caused by the same strains

The nurses were not discharged since such measures would be unjust and probably impede further co operation of personnel in similar situations They were told the re sults and impressed with the importance of obeying to the letter the regulations in the operating theater especially for wearing masks properly over the nose and never remov ing them during operations Subsequently of 50 patients only 2 showed postoperative infections both of the same strains Further efforts regarding asepsis use of double masks and sterile gloves while in the area resulted in fur ther improvement In the ensuing year only 2 more post operative infections occurred neither from the same strains

► [I wonder why they didn t try to eradicate the staphylococcic carrier state in these 2 persons by local or systemic antibiotic therapy —Ed]

Transmission of Staphylococcus Aureus in hospitals was investigated by Ronald Hare and C G A Thomas[6] (St Thomas s Hosp Med School London) Previous reports have implicated the nasal carrier but transfer of organisms from minor staphylococcic infections such as boils styes or acne pimples in staff members may be as important

Cultures were made in 1% Lemco agar with phenolphtha lein diphosphate Most strains of Staph aureus produce aryl *phosphatase with liberation of free phenolphthalein in and* around the colonies This can be detected by a red color when the culture plate is held over a bottle of strong ammonia

The results confirmed previous reports and showed the mechanism of transmitting Staph aureus from the nasal cavity of carriers to other persons is similar to the transmis sion of respiratory tract organisms This is not primarily expulsion of organisms in droplets or droplet nuclei from the anterior nares but an outflow of the organism in the nasal secretions onto the upper lip or alae nasi

Transfer to other persons involves three separate steps (1) Staphylococci are transported by hands handkerchief or any object coming in contact with the nose to the skin clothing bedding and other objects near the carrier (2) Or

(6) Brit M J 2 840 844 Oct. 13 1956

ganisms are released into the atmosphere from friction and dislodgment of dried particles from the skin or hair from spattering of water droplets while washing and from shaking clothing during activity This may occur anywhere in the hospital (3) Infected particles are transported by air currents to nearby persons

Direct expulsions of Staph aureus into free air in droplets or droplet nuclei from the anterior nares is less important than the inevitable presence of the organisms on the skin and clothing of carriers and the release of air borne particles when contaminated surfaces are subjected to friction and movement Alterations in technic designed to prevent staphylococcic infections should encompass this mode of transmission

Problem of Staphylococcic Infections I Host Factors in Experimental Staphylococcic Infections According to Walsh McDermott (Cornell Univ) the degree of exposure to staphylococci in or out of hospitals is no greater today than 12 years ago Staphylococci were plentiful then and are plentiful now

No increase has been noted in the number of patients particularly adults hospitalized with staphylococcic disease and there is nothing to suggest that the forms of the disease seen might represent the dissemination of more malignant strains of the microbe or concentration of more malignant strains in particular localities outside the hospital The one definite improvement in observable staphylococcic disease is the virtual disappearance of serious diseases of primary hematogenous osteomyelitis

Within the special communities of hospitalized patients increased virulence of the so called hospital staphylococci is not evident If the wide range among individual strains of staphylococci in terms of ability to initiate new human disease is considered there is no convincing evidence that hospital staphylococci are more virulent in man than they were However during the last decade staphylococcic disease has developed oftener among patients in hospitals after admission A previously satisfactory equilibrium between hospitalized patients and staphylococci has become unbalanced

The hospital is becoming a favorable breeding place Mod

(7) A N w Yo k Acad S 65 (a t 3) 58 66 1956

riod were infection free When they returned to their usual duties 3 new cases of postoperative infection occurred 2 caused by the same strains

The nurses were not discharged since such measures would be unjust and probably impede further co operation of personnel in similar situations They were told the results and impressed with the importance of obeying to the letter the regulations in the operating theater especially for wearing masks properly over the nose and never removing them during operations Subsequently of 50 patients only 2 showed postoperative infections both of the same strains Further efforts regarding asepsis, use of double masks and sterile gloves while in the area resulted in further improvement In the ensuing year only 2 more post operative infections occurred neither from the same strains

► [I wonder why they didn t try to eradicate the staphylococcic carrier state in these 2 persons by local or systemic antibiotic therapy —Ed]

Transmission of Staphylococcus Aureus in hospitals was investigated by Ronald Hare and C G A Thomas[6] (St Thomas s Hosp Med School London) Previous reports have implicated the nasal carrier but transfer of organisms from minor staphylococcic infections such as boils styes or acne pimples in staff members may be as important

Cultures were made in 1% Lemco agar with phenolphthalein diphosphate Most strains of Staph aureus produce aryl phosphatase with liberation of free phenolphthalein in and around the colonies This can be detected by a red color when the culture plate is held over a bottle of strong ammonia

The results confirmed previous reports and showed the mechanism of transmitting Staph aureus from the nasal cavity of carriers to other persons is similar to the transmission of respiratory tract organisms This is not primarily expulsion of organisms in droplets or droplet nuclei from the anterior nares but an outflow of the organism in the nasal secretions onto the upper lip or alae nasi

Transfer to other persons involves three separate steps (1) Staphylococci are transported by hands handkerchief or any object coming in contact with the nose to the skin clothing bedding and other objects near the carrier (2) Or

(6) Brit M J 2 840 844 Oct 13 1956

erosive neoplasms cut across many barriers to infection

Sixteen patients had had cancer surgery In 4 the cancer was so far advanced that bacteremia could be accepted as merely another factor contributory to inevitable death In 3 the infection and cancer were interdependent and jointly significant In 9 the staphylococcic sepsis was the major disease and in several the only significant disease Of the 16 only 2 survived and were completely free from the infection although in 9 the infection was predominant and in some it was the only disease present In addition to the usual portals of entry cellulitis was apparent at the site of intravenous cannulation in 30 patients

Staphylococcemia was associated with acute leukemia in 23 Normal marrow constituents had been replaced by leukemic cells for at least a month in each patient Peripheral polymorphonuclear leukocyte counts had been repeatedly below 1 000 cells/cu mm for at least a month in 18 and of these 8 survived The influence of ACTH cortisone and similar agents used in treatment could not be ascertained

In the hospital both in personnel and in long term patients there is an appreciable carrier rate of staphylococci that are predominantly drug resistant The patients may be depleted of resistance because of age or neoplastic disease Sustained intravascular introduction of the staphylococci may be of importance in the frequent occurrence of bacteremia in the surgical group of patients Septic thrombophlebitis if it occurs with staphylococcic cellulitis at the site of intravenous cannulation may be responsible for continued bacterial embolization even after cannulation is discontinued If this premise is correct cannulation should be avoided unless absolutely necessary

► [The unusual severity of the staphylococcic infections observed in a hospital for cancer patients supports the views expressed by McDermott in the preceding abstract —Ed.]

STAPHYLOCOCCIC INFECTIONS GENERAL

Acute Staphylococcic Bacteremia Report of Successfully Treated Case is presented by James J Nordland and Craig W Borden[9] Mortality from staphylococcic bacteremia be

(9) Q rt. B ll N rthwest rn Un M S hool 30 133 137 S mm 1956

ern therapy is permitting the survival of persons less able to combat bacterial infection e g insulin treated diabetics children with splenectomies for various hematologic disorders adults with total gastrectomies and some with pulmonary resections Certain common therapy such as cortisone hydrocortisone and ACTH wide acting antimicrobials and x irradiation often create circumstances which facilitate development of infection Conceivably even antihistamines or anticoagulants might influence infection unfavorably To manage many of these modern treatments properly veni and skin punctures must be performed often on the patients most liable to develop infection

We must be aware that the hospitalized patient today is less able to cope with staphylococci Aseptic practices not only in the operating room but in ordinary puncture procedures on the wards should be reviewed and intensified Means must be found for increasing body defenses against staphylococci and for restoring these defenses when they have been reduced

► [This thoughtful discussion brings out some of the important factors in the present day problem of nosocomial staphylococcic infection —Ed]

Staphylococcic Bacteremia Harvey S Collins Alex N Helper Anne Blevins and Gloria Olenberg[8] (Mem l Center for Cancer New York) isolated Staphylococcus aureus (hemolytic mannitol and coagulase positive) from the blood or heart s blood at autopsy 117 times in 73 patients This incidence of staphylococcemia appears uncommonly large compared with that in nearby general hospitals of similar size

Memorial Center which is devoted to the diagnosis and treatment of neoplastic diseases has patients which exemplify certain facets of the general problem of infection specifically staphylococcic disease Patients with leukemia and other neoplasia those treated with irradiation or antitumor chemotherapy may have disturbances of the reticuloendothelial system or other cellular or humoral characteristics which affect ability to resist infection This group comprised chiefly of older persons may be depleted biochemically or nutritionally because of chronic disease or cardiac or renal impairment Wide sweeping surgical procedures or

(8) Ann New York Acad Sc 65 (Part 3) 222 234 1956

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(9) Quart. B II. Northwestern U M School 30 133 137 S mm 1956

fore the advent of sulfonamides was greater than 80% Sulfonamides reduced the mortality and shortly after the introduction of penicillin it dropped to 28% Strains resistant to penicillin and tetracycline derivatives have since appeared and the present mortality is about 50% Staphylococcic bacteremia is still a medical emergency and therapeutic challenge

Physician 32 addicted to Demerol® injected 100 mg into his femoral vein and the next day pain redness and swelling developed The right thigh and calf became swollen and tender and temperature rose to 101 103 F He thought he had thrombophlebitis Eight days before admission he began erythromycin and Aureomycin® but did not improve

On admission temperature was 103 F and the right thigh and calf were indurated red tender to touch and warmer than the left Diffuse superficial venous dilatation was present Homans sign was present Erythromycin and penicillin had no effect on the septic course Blood cultures grew heavy hemolytic Micrococcus pyogenes var aureus coagulase positive A diagnosis of resistant staphylococcic bacteremia was made before the organisms were identified based on the severe septic course unresponsive to therapy Sensitivity studies confirmed resistance to erythromycin and streptomycin but showed sensitivity to chloramphenicol and bacitracin He was given chloramphenicol 3 Gm daily, intravenously and bacitracin 80 000 units daily intramuscularly A deep abscess pocket was aspirated next day Thereafter clinical improvement was moderate and fever was less Eventually recovery was complete

The failure of treatment with penicillin and erythromycin strongly suggested the septic course was due to bacteremia with a resistant organism Since the patient was a physician it could be predicted he would harbor antibiotic resistant micrococci Moreover infection apparently resulted from the pyogenic skin pustule most likely staphylococcic These facts led to the correct assumption of resistant staphylococcus bacteremia

Increasing numbers of erythromycin and penicillin resistant strains of staphylococci now necessitate use of chloramphenicol with or without bacitracin The gravity of staphylococcic bacteremia far outweighs the possibility of bone marrow depression in use of chloramphenicol

Staphylococcic Pneumonia in Adults has long been known as a complication of epidemic influenza and few cases were presented before 1950 unassociated with major influenza During the past 5 years several groups have been re

ported Of 110 cases of pneumonia admitted during 1 year to Hammersmith Hospital 10 were of staphylococcic origin and in only 2 was there serologic evidence of influenza B In a similar report from Belfast only 4 of 15 cases occurred during an influenza outbreak W Hausmann and A J Karlish[1] (Reading Combined Hosp) report 18 cases of staphylococcic pneumonia in adults admitted during 1952 54

There was no local influenza epidemic during this period but virus studies were not made These 18 were 15% of 122 consecutive patients with the diagnosis of primary pneumonia They were aged 16 72 years (average 51) and 11 were males Diagnosis was made when coagulase positive Staphylococcus aureus was predominant in sputum In 12 patients staphylococci were isolated in pure culture in 6 they predominated in a growth of nonpathogenic organisms In 2 coagulase positive staphylococci were grown from the pleural fluid

Six patients had previous chest disease such as chronic bronchitis asthma or recurrent pneumonia 1 had aortic stenosis and another acute nephritis Two cases followed abdominal operations Duration of symptoms before admission was 2 days to 2 months (average 3 weeks) Pleuritic pain was present in 14 of the 18 patients rigors in 4 and herpes labialis in 1 Four produced sticky blood stained sputum

Outstanding features were severity of clinical course and number of serious complications Average hospital stay was 38 days compared with 19 days in other types of pneumonia Abscess developed in 5 patients In the 3 with multiple abscesses the pneumonia was of a wandering type the consolidation moving from area to area and from one lung to the other Empyema occurred in 2 and moderate sterile pleural effusions in 2 Delayed resolution occurred in 12 of the 18 patients None died Response to penicillin closely followed the predicted results as estimated by sensitivity studies Such studies are important

The incidence of staphylococcic pneumonia is increasing In a high proportion of pneumonia cases no pathogenic organisms are grown from sputum on admission probably because of chemotherapy before admission Of the 122 consecutive patients with pneumonia an etiologic diagnosis was

(1) B t M J 2 845 847 O t 13 1956

made for 50 and in 18 of these staphylococci were demonstrated Probably the actual number with staphylococci was higher

Treatment of Staphylococcic Endocarditis Report of Seven Cases Joseph T Melton and Bruce Logue (Emory Univ) saw these 7 patients aged 2-63 since 1951 and 6 were cured Three had rheumatic heart disease and 4 interventricular septal defects The smallest dose used was 30 000 000 units of penicillin and 1 Gm streptomycin daily and the highest 120 000 000 units of penicillin and 2 Gm streptomycin daily except for the patient who died to whom up to 160 000 000 units of penicillin and 1 Gm streptomycin were given daily for 2 months This patient aged 63 had rheumatic heart disease

The treatment of choice in management of staphylococcic endocarditis is penicillin even if there is a history of previous sensitivity In patients in whom the presumptive or proved diagnosis of staphylococcic endocarditis is made the initial therapy should be penicillin in massive doses given in a continuous intravenous drip through a cutdown with booster doses at regular intervals through the infusion tubing Heparin may be added to the infusion to reduce thrombophlebitis at the cutdown site Initially the penicillin dose *should be at least 50 000 000 units by constant intravenous* drip with booster doses of 1 000 000 units every 6 hours In addition erythromycin 500 mg orally 4 times daily streptomycin 1 2 Gm intramuscularly daily and probenecid 0 5 Gm orally 4 times daily should be given

Two more patients were cured with the use of 40 000 000 units of penicillin and 2 Gm streptomycin daily for 4 weeks in one and 22 000 000 units of penicillin and 2 Gm streptomycin daily for 3 weeks in the other

► [Eight cures out of 9 cases of staphylococcic endocarditis is amazingly good The levels of penicillin in the body fluids which would be obtained by such dosages plus probenecid would exceed the levels commonly employed in sensitivity tests Consequently they may have achieved success by using huge doses of penicillin even in the face of unfavorable reports on the sensitivity tests —Eds]

(2) A M A A h Int Med 99 581 586 April, 1957

Antibiotic Treatment of Enteral or Parenteral Salmonella Infections Ivan Saphra[3] (Beth Israel Hosp New York) warns against indiscriminate and widespread use of antibiotics in enteric infections particularly those due to salmonella There is an important difference between salmonelloses confined to the gastrointestinal tract and a generalized salmonella infection after a blood stream invasion Such a generalized salmonellosis septicemia pneumonia meningitis or osteomyelitis constitutes a bacterial invasion into a bacteria free environment by a homologous bacterial agent The pathology symptomatology and treatment of such generalized as well as focal processes are well defined and have been studied extensively

In contrast to these bacteriologically simple situations gastroenteritis is immensely complex There is little knowledge of the sequence of events when a pathogen invades the bacteria crowded gastrointestinal tract and mixes with the gram negative enterobacteriaceae coliforms klebsiella proteus pseudomonas shigella serratia salmonella the gram negative anaerobes of the bacteroides group the gram positive cocci streptococci staphylococci the gram positive aerobes and anaerobes corynebacteria spore formers lactobacilli clostridia yeasts fungi protozoa phages and viruses All these live multiply and die in a nutrient medium enriched with enzymes ferments metabolites toxins and antibodies of changing constitution and pH which may favor one species and inhibit another This symbiotic intestinal flora exists in a medium to which it is adapted and consequently may act antagonistically to a less adapted invader

It is impossible to appraise what happens if into this biologic maze a foreign bacterial element intrudes or if present (as in a carrier) why it suddenly picks up speed to overthrow the normal constituents The situation is further complicated when an antibiotic is added whose action against the individual bacterial strain is little understood The

(3) A t b t M d & Cl Th rap 3 437-438 D mbe 1956

broad spectrum antibiotics are active in vitro against salmonellae and shigellae but their effect in localized gastroenteritis and carrier conditions has been minimal In generalized infections and acute focal manifestations the effect is frequently spectacular

Prolonged and massive treatment with broad spectrum antibiotics severely upsets the bacterial balance in the intestines frequently leading to overgrowth of monilia staphylococci pseudomonas and proteus At best it temporarily inhibits the pathogens which often reappear a few days after the antibiotic is discontinued Sometimes there is even an impression that such prolonged and/or massive antibiotic treatment leads to a generalized infection and sustains diarrhea fever and abdominal distress which disappear after the drugs are discontinued There may be no objection to giving a patient one large oral dose of chloramphenicol oxytetracycline dihydrostreptomycin tetracycline or another broad spectrum antibiotic in an acute gastroenteritis with the aim of cleaning out the intestines in the manner of a laxative but any protracted treatment should be discouraged

► [This discussion by an authority on salmonella bacteria is worth thinking about and his point about the poor results obtained with chloramphenicol in enteritis is substantiated by much clinical evidence In Connecticut several children have developed salmonella enteritis in infancy and continue to harbor the organisms asymptomatically despite many courses of chloramphenicol and other antimicrobial drugs —Ed]

Smoked Fish as a Vehicle of Salmonellosis Annual processing and consumption of smoked fish in the United States amounts to millions of pounds Processing methods have not advanced because many plants are small businesses family owned Instructions to keep these perishable products refrigerated are generally disregarded by retailers White fish and lox are distributed completely unwrapped

I Olitzky A M Perri M A Shiffman and M Werrin[4] (Philadelphia) describe 3 outbreaks of gastroenteritis in which smoked fish transmitted salmonella organisms The smoked fish products were not stored in the showcase but kept on top of the counter The internal temperature of the fish was 70 F Presumably the fish would stay on the counter until sold or otherwise disposed of remaining at room temperature until then contrary to instructions from the processors

(4) Pub Health Rep 71 773 779 August 1956

Most germane to outbreaks was the condition of toilet rooms and handwashing facilities Toilet rooms used by employees in the processing and wrapping operations were remote Water closets barely operated hot water was not provided cold water barely flowed soap and towels were not available and the entire toilet premises were encrusted with a long standing accumulation of dirt Of 70 employees examined 1 was excreting salmonella newport—a woman 30 who had been ill 3 weeks before the outbreaks and wrapped and packed smoked fish 7 hours a day

The public must be educated to the fact that light smokes and salts used in present day smoked fish processing are not in themselves sufficient for safe preservation of fish products

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BACTERIAL ENDOCARDITIS

Murmurless Bacterial Endocarditis G A MacGregor[5] (Postgrad Med School London) reports 4 cases In 3 patients who had subacute bacterial endocarditis aortic incompetence was discovered 8 10 and 12 weeks after onset of symptoms To recognize subacute bacterial endocarditis in its earliest stages some reorientation of ideas is necessary The classic signs were formulated when the disease was incurable and are manifestations of its later complications

Most of the exceptional patients without heart murmurs like those here described eventually show aortic incompetence and are considered to have bicuspid valves Average duration of symptoms before hospitalization is 10 weeks This interval is long enough for valve lesions to appear

CASE 1—Man 39 had sudden fever with severe malaise and headache After 2 weeks illness he was hospitalized with temperature 103 F and a tachycardia but no other findings a normal white blood cell count and an elevated sedimentation rate Blood culture revealed beta hemolytic streptococcus After penicillin therapy the temperature returned to normal on the third day By the fourth day a soft aortic diastolic murmur was heard Heart failure developed but he recovered and was discharged Six years later he had a second attack of subacute bacterial endocarditis following a tooth extraction Although the first infection was virulent enough to produce severe valve damage a murmur did not appear until the 18th day of illness

(5) B t M J 1 1011 1013 M y 5 1956

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(4) Pub Health Rep 71 773 779 August, 1956

On the belief that teeth, good or bad, present a great danger to the patient with this disease, all teeth were removed in 7 patients who had at least one attack. The number is inadequate to prove anything, but so far none has relapsed after 1[illegible] months to 7 years, although the expected relapse rate is 1[illegible].

Whether the infection ever occurs in an edentulous patient is unknown, but no published paper has specifically referred to such a case, nor has any physician with vast experience remembered one. From the present evidence the evidence overwhelmingly incriminates the teeth as the chief source of the infection. So long as teeth or fragments of teeth remain in the jaw, a formidable but preventable hazard is ever present, and all patients with this type of infection should have compulsory complete dental clearance as an essential part of therapy.*

DENTAL STATE ACCORDING TO AGE GROUPS

	5–9	10–19	[illegible]	[illegible]	[illegible]	[illegible]	60–69	[illegible]	[illegible]
Control group									
No. of patients	11	27	50	40	3	42	45	9	[illegible]
No. edentulous	0	1	3	10	21	25	3	[illegible]	129
% edentulous	0.0	4	6	20	[illegible]	6[illegible]	—	[illegible]	
S.B.E. due to S. viridans									
No. of patients	1	3	14	13		2	4	1	43
No. edentulous	0	0	0	0	0	0	0	0	0
Expected no. edentulous	0	0.12	0.84	2.6	2.0	1[illegible]	[illegible]	[illegible]	[illegible]
S.B.E. due to other organisms									
No. of patients	0	0	4	2	4	0		1	1
No. edentulous	—	—	1	1	3	—	3	[illegible]	8
Expected no. edentulous	—	—	0.2[illegible]	0.4	1.2	—	[illegible]	[illegible]	[illegible]

* [This seems a radical doctrine but the author makes a good case for it. Certainly there is a real chance of a second attack in a person who has recovered from bacterial endocarditis, and prophylactic chemotherapy as employed against rheumatic fever [illegible] against this disease.—Ed.]

Subacute Bacterial Endocarditis in a Penicillin-Sensitive Patient Successfully Treated with ACTH, Chlor-Trimeton* and Penicillin, [illegible] reported by Joel [illegible] B[illegible] and Alfred Lubart ([illegible])

(7) New York [illegible] M. [illegible] May [illegible]

CASE 2 —Man 54 had pyrexia for 6 weeks unaffected by antibiotics On admission he was anemic febrile and had an elevated sedimentation rate and white blood cell count Two weeks later a soft aortic diastolic murmur was heard and a penicillin sensitive streptococcus was found on blood culture During the first week of penicillin treatment he developed an Osler node and pain suggestive of a splenic infarction but eventually recovered

CASE 3 —Man 35 had aching muscles fever and a sore throat He received two short courses of chlortetracycline but pyrexia recurred after each Mild pyrexia and myalgia persisted A soft diastolic aortic murmur was heard and Streptococcus viridans grew from the blood 2 3 months after onset of symptoms The spleen was not palpable Penicillin was given and recovery was prompt

CASE 4 —Man 54 had sudden fever with transient weakness of the left arm and leg Sedimentation rate and white blood cell count were elevated He had had two attacks of pleurisy in the previous 3 months with pain in the shoulder and sweats both treated with penicillin One week later the left shoulder pain recurred followed by rigors During one of the attacks he suddenly became aphasic and on hospitalization was found to have a right hemiplegia A presumptive diagnosis of infective endocarditis was made blood was cultured and treatment with penicillin started Streptococcus viridans was recovered A basal systolic murmur was heard first 1 week after therapy was initiated This patient probably had infective endocarditis for at least 3 months before the murmur was heard The so called pleurisy was almost certainly caused by emboli in the spleen or elsewhere On admission the sedimentation rate was higher than should be expected after only 5 days illness He had no anemia

► [We also saw 2 cases like this during the past year middle aged men with fever and Streptococcus viridans bacteremia who first exhibited the murmur and peripheral signs of aortic insufficiency some days after they came under observation The old dictum No murmur no s b e needs to be employed with reservations —Ed.]

Teeth Streptococcus Viridans and Subacute Bacterial Endocarditis F G Hobson and B E Juel Jensen[6] (Radcliffe Infirm Oxford England) studied the clinical records of 59 patients hospitalized for subacute bacterial endocarditis between 1945 and 1955 In 43 it was due to Streptococcus viridans and in 16 to other organisms

When the dental status was studied and compared with 315 unselected controls it was noted that subacute bacterial endocarditis due to proved or presumptive infection with Str viridans never occurred in a patient who was edentulous i e who had full dentures and no visible teeth (table) A definite history of dental extraction preceded onset of the initial attack in 7 of the 43 patients

(6) Brit M J 2 1501 1505 D 29 1956

how many blood cultures were required for positive results In 52 of the 82 cases diagnosis was made on the first culture In only 6 were more than 5 cultures necessary Of these 6 cases 5 were due to organisms other than Streptococcus viridans and in 3 previous treatment with penicillin had been given In no case was more than 10 cultures necessary for diagnosis Of all cultures drawn 41% were positive

Thus it is reasonable to begin therapy in a suspected case of bacterial endocarditis after a limited number of blood cultures have been drawn The evidence supports Libman s concept of a definite abacterial phase in certain cases If 5 blood cultures are already negative the chance of obtaining a positive result is considerably decreased This is important in regard to the time for beginning therapy

Tubercle Bacillus Bacterial Endocarditis Developed on a Surgical Mitral Sling Rarely has a case been reported in which tubercle bacilli multiplied on or caused vegetations of diseased or normal cardiac valves or on the endocardium Considering the frequency of hematogenous dissemination of tubercle bacilli the rarity of true tubercle bacillus bacterial endocarditis is peculiar A case is reported by R Patterson Russell Morgan Berthrong and Autrey R Croke[9] (Colorado Springs)

Woman 31 had a history of St Vitus dance and joint and cardiac manifestations In February 1952 she had a transventricular pericardial tamponage in which a tube of pericardium was inserted across the ventricular side of the mitral valve orifice through small incisions in the anterior and posterior left ventricular wall She had little objective improvement

In August 1953 congestive failure reappeared and petechiae of the skin were noted She had no fever or leukocytosis but 3 blood cultures grew hemolytic Staphylococcus aureus She was given 3 600 000 units of penicillin daily for 6 weeks and thereafter blood cultures were consistently negative In November 1953 petechiae reappeared associated with weakness and anorexia Fever was again absent and the white blood cell count normal but hemolytic Staph. aureus was again cultured from the blood and she was again apparently cured by 6 000 000 units of penicillin a day for 6 weeks In June 1954 she was admitted with a typical septic fever (between 101 and 104 F) The spleen became palpable no petechiae were seen Th white blood cell count rose to 18 000 She was given intravenous penicillin oral streptomycin and a blood transfusion but died 4 days after admission

(9) Bull. J hns Hopki H p 99 96-308 November 1956

Man 44 was hospitalized with a second typical attack of sub acute bacterial endocarditis The fir t episode in which blood cul tures were positive tor Staphylococcus aureus was successfully treated with 8 000 000 20 000 000 units ot penicillin daily for 4 week The econd attack occurred 6 months later after extraction ot a tooth At this time repeated blood cultures were positive for Streptococcus viridans

An initial parenteral injection of 1 000 000 units of penicillin was followed by generalized urticaria and mild shock Oxytetracycline was then substituted 2 Gm daily tor 34 days and he was discharged asymptomatic with repeated sterile blood cultures Ten days after discharge Str viridans was cultured from the blood Chlor Tri meton® was injected with each dose of penicillin but reactions similar to those with the first dose ot penicillin occurred Erythro mycin about 5 Gm daily was ineffective since blood cultures re mained positive after 16 days of therapy and the temperature spiked daily

ACTH 20 units every 6 hours subcutaneously was maintained for 3 days Penicillin was then reinstituted along with Chlor Trimeton® in gradually increasing desensitizing doses The peni cillin dose was gradually increased to 1 000 000 units every 2 hours without ill effects even though ACTH was discontinued after 5 days Penicillin was maintained at maximum dosage for 6 weeks and blood cultures remained negative for 12 months of follow up

Chlor Trimeton® alone was unsuccessful in desensitizing to penicillin but ACTH therapy before a second attempt allowed the combination of Chlor Trimeton® and increas ing doses of penicillin to be used without ill effects

This case points up failure of bacteriostatic drugs (eryth romycin and oxytetracycline) to cure the infection even in large doses and despite a high degree of susceptibility to the e drugs in vitro

Penicillin is the drug of choice in Str viridans subacute bacterial endocarditis even in patients who are sensitive to penicillin

► [The lesson is worth repeating tetracyclines erythromycin and chlor amphenicol rarely eradicate bacterial endocarditis most of the favorable results are obtained with penicillin—Ed]

Number of Blood Cultures Necessary to Diagnose Most Cases of Bacterial Endocarditis Ideally the causative or ganism should be identified in each case of endocarditis but the clinician often does not know how long to wait before beginning therapy James Belli and Burton A Waisbren[8] (*Marquette Univ*) reviewed 82 cases of subacute bacterial endocarditis in which bacteria were cultured to determine

(8) Am. J M Sc 232 84 288 Septembe 1956

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Tubercle Bacillus Bacterial Endocarditis Developed on a Surgical Mitral Sling Rarely has a case been reported in which tubercle bacilli multiplied on or caused vegetations of diseased or normal cardiac valves or on the endocardium Considering the frequency of hematogenous dissemination of tubercle bacilli the rarity of true tubercle bacillus bac terial endocarditis is peculiar A case is reported by R Pat terson Russell Morgan Berthrong and Autrey R Croke[9] (Colorado Springs)

Woman 31 had a history of St Vitus dance and joint and cardiac manifestations In February 1952 she had a transventricu lar pericardial tamponage in which a tube of pericardium was inserted across the ventricular side of the mitral valve orifice through small incisions in the anterior and posterior left ventricu lar wall She had little objective improvement

In August 1953 congestive failure reappeared and petechiae of the skin were noted She had no fever or leukocytosis but 3 blood cultures grew hemolytic Staphylococcus aureus She was given 3 600 000 units of penicillin daily for 6 weeks and thereafter blood cultures were consistently negative In November 1953 petechiae reappeared associated with weakness and anorexia Fever was again absent and the white blood cell count normal but hemolytic Staph aureus was again cultured from the blood and she was again apparently cured by 6 000 000 units of penicillin a day for 6 weeks In June 1954 she was admitted with a typical septic fever (be tween 101 and 104 F) The spleen became palpable no petechiae were seen The white blood cell count rose to 18 000 She was given intravenous penicillin oral streptomycin and a blood transfusion but died 4 days after admission

(9) B ll J h Hopk H p 99 296 308 N mb 1956

Autopsy showed mitral valve deformity The sling virtually filled the mitral valve orifice Its surface was smooth save for several firm fibrous pedunculated vegetations 0 2 0 5 cm attached to the inferior surfaces of the intraventricular portion of the sling One polypoid friable smooth vegetation was hanging down from its attachment deep in a crypt between the sling and posterior papillary muscle The parenchyma of the lungs was studded with 1 2 mm gray nodules The spleen weighed 530 Gm The surface of the kidneys had a flea bitten appearance

Acid fast stains of the vegetations showed enormous numbers of acid fast bacilli lying singly and in colonies *often forming distinct cords through all areas of the vegetation* No tubercles or giant cells were present Tiny tubercles typical of miliary tuberculosis were seen in the epicardium and endocardium in other sections of the left ventricle Numerous sections of the lung revealed small uniformly distributed tubercles composed of epithelioid cells and Langhans giant cells with caseous centers Occasional acid fast bacilli were found in these tubercles

No doubt this patient s extremely malformed mitral valve and the surgically created sling became repeatedly infected and cured of a common bacterial organism Then tubercle bacilli from the older pulmonary lesion were probably implanted on a vegetation and slowly multiplied to *enormous numbers* *The final acute episode was massive* hematogenous spread most likely from the valvular tuberculosis

All aspects indicate that this case was one of true tubercle bacillus bacterial endocarditis The huge colonies of typically acid fast bacilli growing in cord formations deep in the acellular vegetations were probably present for weeks before the miliary tuberculosis occurred

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URINARY INFECTIONS ACQUIRED IN HOSPITALS

Urinary Tract Infections Caused by Antibiotic Resistant Coliform Bacilli William M M Kirby Douglas O Corpron and Donald C Tanner[1] (Seattle) in a survey of urine cultures of 85 patients with urinary tract infections found coli form bacilli to be predominant In 41 patients the organisms were sensitive and in 44 resistant to antibiotics Striking differences were observed between the two groups

(1) J A M A 16 1-4 Sept 1 1956

The patients with organisms sensitive to antibiotics had in general acute urinary tract symptoms on admission The incidence of obstructive lower urinary tract disease was low and few patients had had recent catheterizations The patients with resistant bacteria had a high incidence of recent urinary tract instrumentation Many had entered the hospital without infection and the urine had become cloudy and infected only after an inlying catheter had been in place for several days The incidence of underlying urinary tract obstruction was relatively high Only 6 of the 44 patients had probably been treated with all the chemotherapeutic agents to which the bacteria were resistant

Coliform bacilli rarely acquire antibiotic resistance during therapy of individual patients Yet laboratory surveys indicate a relatively high percentage of all coliform bacteria isolated from urine cultures are resistant to a number of chemotherapeutic agents These resistant bacteria are acquired in the hospital chiefly by patients with indwelling catheters Their source is unknown Possibly the catheters themselves are contaminated Another possibility is that coliforms are carried in the nasopharyngeal flora of hospital personnel the same as micrococci Most likely the objects with which the patient comes into close contact particularly mattresses and blankets are heavily contaminated with resistant coliforms

It is likely that hospital acquired infections with antibiotic resistant coliforms are widespread and unrecognized Recent reports from other laboratories in hospitals show that one third or more of isolated coliform bacteria are antibiotic resistant

► [It appears that the situation here is analogous to that with staphylococcic infections infections acquired in the hospital are likely to be due to coliforms which are resistant to commonly employed antimicrobial agents —Ed]

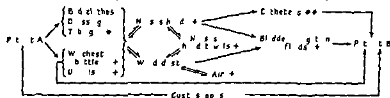
Urinary Tract Infection in Male Urologic Ward There are two possible modes of infection autoinfection by the patient s intestinal flora or cross infection If autoinfection were common organisms in the urine should also be present in the feces If cross infection were the cause organisms should be recoverable from sites whence they could be transmitted to patients A A C Dutton and Mary Ralston[2]

(2) La et 1 115 119 J 19 1957

(Postgrad Med School London) investigated both possi bilities

Of 42 patients with prostatism 24 became infected in the hospital 13 were infected when admitted and 6 remained uninfected Of 38 other patients 11 became infected and 11 were infected when admitted Nearly all who became in fected in the hospital showed infection a few days after in sertion of an indwelling catheter or other instrumentation

Evidence for cross infection was strong Of 22 patient infected with Staphylococcus pyogenes 11 were by the same



F g 1 —P s ble route of ross infection * tube lead ng f om cath t r to W ch t bottl s t st m d nd no a v org n m isolated + t ts m de a d u ry tr ns s lated (Cou tesy of D tt A A C d Ralsto M Lan et 1 115 119 Jan 19 1957)

phage type ot 9 with klebsiella 7 were the same strain of 11 with Proteus mirabilis 8 were the same strain One strain of each species of providence Proteus vulgaris and Esch erichia freundii infected 17 14 and 4 patients respectively These organisms were rare in urinary infections elsewhere in the hospital In this series they were isolated only from urine of patients who became infected after admission Drug sensitivity was characteristically that of hospital infection

If the cause were autoinfection since the organisms were antibiotic resistant they must have appeared in the intes tines after admission The presence of the same strain in many patients indicates cross infection by some route Therefore if autoinfection took place it was subsequent to ingestion of infecting organisms and not due to chemother apy However urinary strains were absent from any fecal samples taken before urinary infection developed or on the same day as the first infected specimen of urine was found Also there were no E coli infections contrary to the ex pected high incidence if infections had arisen in intestinal tracts Presumably they were exogenously acquired Pos sible routes of cross infection are indicated in Figure 1

The same species isolated from patients urine were re covered from bottles used to collect urine from indwelling catheters urinals ready for reuse nurses communal hand towels nurses hands solutions for bladder irrigations air and ward dust but not from catheters or cystoscopes Ward dust and air are a permanent reservoir of species that infect the urinary tract

Some contamination of nurses hands seems inevitable but it is an important cause of cross infection The risk of some procedures e g bladder irrigation is obvious but in cidental procedures such as reconnecting the drain tube might also transfer organisms to the patient Cross infection of the urinary tract has special significance now that an in creasing proportion of hospital strains of bacteria are resist ant to antibiotics

► [This good piece of work lends support to the assumptions made in the preceding abstract.—Ed]

Entry of Bacteria into Urinary Tracts of Patients with Inlying Catheters Although bacteria are frequently intro duced into the bladder when catheters are inserted urinary tract infections are much less common after single catheter izations than after constant drainage of the bladder with inlying catheters Edward H Kass and Lawrence J Schnei derman[3] (Harvard Med School) demonstrated the appear ance in urine of bacteria which were applied to the periure thral epithelium of patients with inlying catheters Three patients with indwelling urethral catheters had Serratia marcescens applied to the glans or vulva In 24-48 hours the organisms were cultured from bladder urine

The precise pathway is unproved but the organisms may migrate by way of the fluid filled thin space between the catheter and urethral mucosa When a catheter has been in place 12 24 hours or more this space is almost always filled with a watery grayish green fluid probably a mixture of urine and exudate Such fluid might provide an excellent culture medium in which bacteria might multiply and spread from the exterior to the interior of the urinary tract

► [A neat demonstration of the fact that the pathway to bladder infection is around the outside not through the lumen of the indwelling catheter —Ed]

(3) N w E gland J M d 256 556-557 M 1 1957

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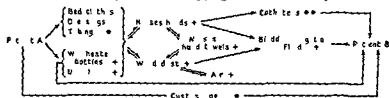


Fig 1—Possible routes of cross infection tube lead g from catheter to Winchester bottles tests made and n urinary organism isolated + tests made and urinary st isolated (Courtesy of Dutton A A C and Ralston M Lancet 1 115 119 Jan 19 1957)

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is a self limited disease All symptoms and complications are reversible and if cured patients leave the hospital without sequel To avoid the long continued psychologic strain of the disease H C A Lassen Erik Henriksen Frits Neukirch and Henning Sund Kristenson[5] (Copenhagen) gave nitrous oxide anesthesia continuously for 5 or 6 days This is danger ous therapy In each case it induced bone marrow depres sion Aplastic anemia developed in 2 patients and both died of overwhelming bacteremia

Conventional treatment for tetanus is administration of barbiturates chloral hydrate or bromethol If spasms are not suppressed or secretions accumulate in upper respira tory passages high tracheotomy under general anesthesia is indicated This prevents suffocation due to laryngeal spasm or tetanic standstill of respiratory muscles and allows as piration of secretions Convulsions and rigidity can be con trolled by d tubocurarine chloride intravenously Artificial respiration may be required

The extensive literature on nitrous oxide contains no in formation about its toxic effect on bone marrow and it has been considered innocuous This applies only to its usual surgical use and not to its continuation over many days Prolonged use of nitrous oxide may cause acute aplasia of the bone marrow

TUBERCULOSIS

Efficacy of BCG Vaccination Epidemic of Tuberculosis in State School with Observation Period of 12 Years Tage V Hyge[6] reports the occurrence of an explosive epidemic of tuberculosis in 1943 in a Danish state school with 368 girls This epidemic chanced to fulfil most requirements for a con trolled experiment

Of 105 tuberculin negative pupils 94 were exposed to in fection Of these 70 became tuberculin positive 41 showed evidence of primary tuberculosis and 14 developed postpri mary progressive pulmonary tuberculosis after a latency pe riod of up to 10 years (15% of those exposed)

Of 133 pupils previously vaccinated with BCG 106 were

(5) Lancet 1 527 530 Apr 28 1956
(6) Act tuberc. scandina 32 89 107 1956

Leptospirosis as Major Cause of Short Term Pyrexia in Tropical Environment Fred R McCrumb Joe L Stockard and T E Woodward[4] studied febrile diseases of short duration in 614 military personnel and 238 indigenous civilians in Malaya Leptospirosis accounted for 35% in the military group and 13% of the civilian group Scrub typhus malaria and illnesses serologically related to dengue accounted for most of the others About 30% of the illnesses remained unclassified

Of the 244 patients with leptospirosis 209 had detailed clinical study In Malaya this was an acute self limiting disease of approximately 8 days of fever with extremes of 4-13 days Onset was abrupt in 70% with fever gastrointestinal disturbances headache cough myalgia retrobulbar pain and photophobia Physical signs were conjunctival injection in 85% lymphadenopathy in 50% muscle and abdominal tenderness in 50% nuchal rigidity in a third and in 6 of 10 patients studied a lymphocytic pleocytosis of 40-400 cells/cu mm and slight elevation of cerebrospinal fluid protein In most patients total blood leukocyte count was normal

Diagnosis of leptospirosis was established in 228 patients by demonstration of the organism in blood or a positive complement fixation or agglutination lysis test Of 182 cases in which isolation of the organism was attempted leptospiremia was demonstrated in 108 (59%) These represented 13 different serogroups

Based on observations made on 5 military units entering a high endemic area the rate at which a susceptible group of soldiers contracts leptospirosis under combat conditions is proportional to the length of exposure during jungle operations

TETANUS

Treatment of Tetanus Severe Bone Marrow Depression after Prolonged Nitrous Oxide Anesthesia Severe tetanus

(4) Trans A Am Phys 12 s 69 1 2 130 1956

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Of 133 pupils previously vaccinated with BCG 106 were

(5) La et 1 527 530 Ap 29 1956
(6) A ta tube sc nd 32 89 107 1956

exposed to infection under the same conditions as the pupils who were tuberculin negative None had evidence of primary tuberculosis and only 2 developed progressive pulmonary tuberculosis (1 9% of those exposed)

Thus postprimary pulmonary tuberculosis was 8 times as frequent in the negative group as in the BCG vaccinated group (15 1 9) and total incidence was 23 times as high among the negative as among the BCG vaccinated (44 6 1 9) group

Of 130 tuberculin positive pupils 105 were exposed to infection and 9 of these developed progressive pulmonary tuberculosis after a latency period of up to more than 8 years Two or three of these cases may have been due to exogenous reinfection Thus 23 cases of postprimary progressive pulmonary tuberculosis occurred in the initially tuberculin negative and tuberculin positive groups compared with 2 cases in the BCG vaccinated group

It is evident that the most effective protection—not only from primary but from late postprimary pulmonary tuberculosis—is BCG vaccination

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FUNGOUS INFECTIONS

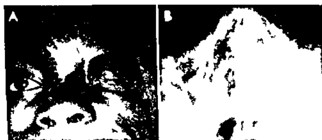
Mucormycosis—A New Disease? Although this is a new disease for the United States cases have been observed in all parts of this country Canada and England and its occurrence is probably world wide It is usually a complication of other diseases diabetes mellitus leukemia multiple myeloma fatal burns and cirrhosis It is caused by fungi common in nature and as laboratory contaminants and not usually considered pathogens Spread of the fungus is unique for micro organisms because it is via the arteries It penetrates the tough muscular walls grows within the lumens and stimulates purulent arteritis or thrombosis Later it invades veins and lymphatics Vascular occlusions and resulting infarctions are characteristic This fungous infection is notable among mycoses because it is acute rather than chronic

Roger D Baker[7] (Duke Univ) reports a case (Fig 2) in

(7) J A M A 163 805 808 Mar 9 1957

which the fungus appeared to enter by the nose producing sinusitis orbital cellulitis and thrombosis of the ophthalmic and internal carotid arteries Thirteen similar cases have been reported since 1943 in patients aged 5 months to 65 years without sex or race differential Seven had diabetes mellitus The fungus permeates the fat nerves perineural lymphatics and veins of the orbit In several patients the fungus produced brawny red induration of the cheek Mucor mycosis of the paranasal sinuses and orbit may develop without cerebral lesions with clinical recovery

Pulmonary mucormycosis may be primary or hematoge nous The former represents fungus growth in the bronchi



F g 2—M my *A* o b tal swell g of l ft y *B* l t ral s t s (Co t y f B ker R D J A M A 163 805 808 M 9 1957)

in which organisms penetrate the bronchial walls and infect the hilar tissues then invade the pulmonary artery and vein causing thrombosis and pulmonary infarction Onset may be sudden with severe chest pain pleural friction rub and bloody sputum However consolidation may form insidi ously Fever and leukocytosis are present Duration of the mycosis in the 10 reported cases all fatal was 3 30 days Pulmonary mucormycosis appeared as the main cause of death in 6 and as an incidental finding in 4 Lesions of pul monary mucormycosis do not respond to antibacterial agents

Intestinal mucormycosis appears as hemorrhagic seg ments in the ileum or large intestine In 2 cases the largest hemorrhagic and ulcerative lesions were in the terminal section of the ileum A disseminated form with lesions in many organs has been reported

Diagnosis of mucormycosis may be made by examination of tissue specimens biopsy or autopsy Diagnosis should be possible by examining sputum cerebrospinal fluid or exudate Culture of rhizopus is corrobative Since rhizopus is a common contaminant recovery of this organism in culture is not in itself diagnostic

► [This doesn t seem to be a really rare disease now and we are going to hear more about it because of its curious tendency to affect patients with diabetes and leukemia —Ed]

Case of Trichophytia Simulating Furunculosis is reported by B J Torheim and S D Henriksen[8] (Oslo) The species of the genus Trichophyton can invade the keratinous tissues of animals and man predominantly through the nails hair and skin The commonest manifestation in the skin is the annular erythematous papulosquamous lesion The central area is scaly and the advancing active periphery usually is studded with crusting vesicles and pustules

Careful bacteriologic examination is essential in each case *In the case reported examination for fungi had not been* suggested and despite the fungous infection in the nails none of the attending physicians suspected fungous etiology The lesions looked like common staphylococcus boils and did not actually indicate trichophytia

Girl 19 from a rural area had numerous furuncle like lesions in the distal calves mainly just above the ankles for 2 years The furuncles were bluish red and contained yellow sticky thick pus and left solid infiltrations and small scars in the skin New pustules appeared constantly without pain or tenderness She had been treated with antibiotics and several attempts had been made to prepare an autogenous vaccine Staphylococci were never cultured from the lesions No bacteria were seen by microscope However a careful study of gram stained films revealed a few fungus like elements and numerous mycelium threads in preparations of potassium hydroxide solution indicated some species of trichophyton The finger nails and particularly the toenails were porous and deformed suggesting a long standing fungous infection Trichophyton mentagrophytes was isolated from the nails and skin lesions The infection probably spread from the toes

Outbreak of Unusual Form of Pneumonia at Camp Gruber Oklahoma in 1944 Follow up Studies Implicating Histoplasma Capsulatum as Etiologic Agent The outbreak had a common source and a high attack rate and most of the patients revealed extensive and protracted pulmonary infiltra

(8) A ta path et m rob 1 scand n 39 353 356 December 1956

tion It was recognized by A E Feller Michael L Furcolow Howard W Larsh Alexander D Langmuir and John H Dingle[9]

All 27 patients had entered an abandoned storm cellar during field maneuvers 12 days before onset of disease Studies at that time failed to reveal a cause The illness was characterized by sudden constitutional symptoms substernal pain and chest constriction Most were severely ill for 2-4 weeks with remittent fever of 104 106 F and mild cough Chest films showed extensive mottled infiltrations of a uniform pattern with multiple lesions 1 20 mm in diameter scattered diffusely and symmetrically throughout both lung fields

Improvement began during the 3d or 4th week after onset In a few patients the fever continued for 6 weeks Pulmonary lesions remained static for about 2 months At the end of 7½ months 21 patients had required release from the armed service because of illness and were still complaining of severe fatigue weakness and pain in the thorax after mild exercise

Comprehensive studies provided increasing evidence that the epidemic was due to H capsulatum Further interest arose when numerous cases of miliary pulmonary calcification were noted in Kansas City school children In all children skin tests gave positive reaction to histoplasmin and negative reaction to tuberculin and H capsulatum in the active stage was isolated from one child

Ten years after the epidemic serologic tests were done on serums collected at the time of the epidemic Complement fixation and precipitation technics revealed antibodies to H capsulatum antigens in the serum from each person involved in the epidemic

Follow up studies were done on 26 of the 27 patients of whom 13 were receiving veterans compensation and 15 reported the persistence of pulmonary symptoms presumably due to the illness The most striking findings were in chest x rays which revealed miliary calcification involving all lobes During the acute illness chest films had shown disseminated pneumonitis which later tended to become nodular

(9) Am J M d 2f 184 19 A gu t 1956

The accumulated evidence and follow up studies indicate clearly that the 1944 outbreak at Camp Gruber was caused by H capsulatum

► [Quite a number of small epidemics of acute pneumonitis followed years later by miliary calcifications have now been shown to have been due to histoplasmosis —Ed]

Hydroxystilbamidine Treatment of North American Blastomycosis In 1939 systemic blastomycosis was fatal in 92% of cases In the past few years attention has been focused on a new group of drugs in systemic and deep mycotic infections—the aromatic diamidines They are effective in several diseases including trypanosomiasis leishmaniasis and multiple myeloma

Treatment with stilbamidine has not always succeeded in blastomycosis and trigeminal neuropathy may develop from its use but 2 hydroxystilbamidine does not produce this side effect Irving D London[1] (Montgomery Ala) reports 4 cases 2 cutaneous and 2 systemic apparently arrested by the latter drug

CASE 1 —Woman 48 had an eruption on the left leg The diagnosis was made the next month and she received successively *iodides blastomyces vaccine x ray treatments and local applica*tions Four months after onset she had typical cutaneous granulomatous lesions of blastomycosis over the left leg and parts of the left thigh and right leg Smears from the moist border revealed double contoured bodies with budding pathognomonic of Blastomyces dermatitidis For the next 4 months she received two courses of hydroxystilbamidine intravenously totaling 5 025 Gm The lesions began to heal during the first course and completely healed during the second leaving a normal skin from which no organisms could be cultured She remained well for the 9 months of follow up

CASE 2 —Man 33 noted a small lump in the left calf which ulcerated *Smears revealed the double contoured organisms of* B dermatitidis but they could not be cultured A total of 6 06 Gm hydroxystilbamidine was given in two 14 day courses The ulcer began to heal within 5 days and was healed by the end of the first course

CASE 3 —Youth 19 was admitted for removal of a coin lesion of the lung which grossly resembled tuberculoma Smears revealed single budding thick walled spores of B dermatitidis which grew from lung cultures and three sputum cultures Hydroxystilbamidine 11.25 Gm in a 50 day course was given He remained asymptomatic and chest x rays were clear a year after therapy

CASE 4 —Man 45 had pleural effusion for 1 month Sputum cultures showed B dermatitidis He received 9 8 Gm hydroxystilbamidine in 43 days with symptomatic improvement and slow but steady regression of the effusion and pneumonitis

(1) South M J 49 1098 1103 Oct ber 1956

Most noteworthy are the rapid action of hydroxystilbami dine on the course of blastomycosis and the absence of neu rotoxicity of this drug

Treatment of Moniliasis with Nystatin Edwin T Wright James H Graham and Thomas H Sternberg (Univ of Cal ifornia) treated 122 patients 42 with oral moniliasis 17 with vaginal moniliasis and 63 with cutaneous involvement such as paronychia intertrigo and perleche

Nystatin was applied topically as ointments solutions powders troches capsules and suppositories and jelly for vaginal use The ointment and gel consisted of a plasticized petrolatum base (Plastibase®) containing 5 000 200 000 units of nystatin/Gm of ointment The solutions contained 5 000-100 000 units/cc One solution was propylene glycol and another was 2% procaine hydrochloride and 0 25% poly sorbate 80 with and without 2 5 mg hydrocortisone/cc The powder contained 175 000 units of nystatin/teaspoon Each troche contained 2 000 units of nystatin in addition some troches contained 2 5 mg neomycin sulfate and 0 25 mg gramicidin Capsules and tablets used as troches and suppositories contained 125 000 500 000 units The supposi tories for vaginal use contained 10 000 100 000 units with some containing an additional 2 5 mg neomycin sulfate and 0 25 mg gramicidin

Of the 122 patients with proved moniliasis treated with nystatin lesions healed promptly in 53 slowly in 64 and more slowly in 5 None developed allergic contact derma titis or primary irritation after treatment Effectiveness was influenced by the vehicle In an ointment on intertriginous areas nystatin gave poor results but in solution it was rap idly effective

Infections Due to Candida Albicans in Infants and Chil dren have been receiving more attention recently because of their increasing frequency and effective treatment with new fungicidal drugs Robert Debre Marcel Lelong P Mozzi conacci J Robineau Le Tan Vinh R Grunbach and R Habib[3] report recent observations on 41 patients includ ing histologic studies in 2 fatalities

Candida infections are of two types mucosal and visceral Stomatitis is the most frequent superficial infection com

(2) J A M A 163 92 94 J 12 1957
(3) Ann. péd t 33 731 750 F b 2 1957

monly manifested by muguet (thrush) but it may be erythematous or pseudomembranous or assume the appearance of black tongue It often extends to the esophagus eventually involving the stomach and may finally be localized in the intestines Extension to the larynx and tracheobronchial tree is doubtless a frequent complication of buccopharyngeal thrush pulmonary localizations are also possible but cannot be confirmed solely by finding of the fungus in the sputum

Visceral infections are propagated through the blood Generalized moniliases can be suspected when the fungus is found in the urine they can in some cases be demonstrated by blood culture More often septicemia is revealed by development of metastatic lesions in different viscera Among these localizations the most serious are meningitis and endocarditis Subcutaneous abscesses due to the fungus probably result from dissemination through the blood stream

Histologically visceral lesions assume the form of inflammatory granulomas with an abundance of yeastlike cells and mycelic filaments Fungi of the genus Candida are ordinarily saprophytes especially of buccal and rectal mucosa In the female the vaginal mucosa is a frequent site of this infection, especially during pregnancy Contamination of the newborn during delivery is probably frequent Candida albicans does not appear on the skin except in pathologic cases

Incrimination of antibiotics in the development of candida infections has been predicated on coincidence of the current increase in moniliases with wider use of antibiotics Experimental studies have partially confirmed this hypothesis

The presence of candida in a biopsy specimen cannot be considered pathologic except when fungus cells are predominant with respect to microbial flora when even in the presence of an abundant microbial flora more than a few yeastlike cells are found per microscopic field and when in cultures of ordinary mediums yeast cells develop exclusively or predominantly

Nystatin (Mycostatin®) is an efficacious antifungic antibiotic The usual dosage is 1-4 crushed tablets of 500 000

units There is also a pomade containing nystatin and an injectable solution is being developed In 25 patients treated by the authors mycosis was cured in 17 with negative biopsies in 3 8 days In 5 in whom moniliasis recurred sometimes repeatedly nystatin was effective during recurrences No instance of resistance of C albicans to the drug has been seen In 3 patients treatment failed despite adequate dosage possibly because of coexisting infection

The importance of maintaining local contact of nystatin with the lesions of buccal muguet is stressed together with systemic treatment and prophylaxis Precautions should be taken to avoid transmission of C albicans by the hands toilet objects or through the air

Fatal Systemic Moniliasis Following Pancreatitis Beach Barrett Wade Volwiler William M M Kirby and Clyde R. Jensen[4] (Univ of Washington) report a patient who developed peripancreatic abscess during acute pancreatitis A prolonged course of broad spectrum antibiotics probably suppressed the normal bacterial flora of the large bowel which allowed overgrowth of Candida albicans This organism apparently spread to the necrotic tissue surrounding the pancreas and via the blood stream to the kidneys and myocardium

Man 68 was admitted for severe abdominal pain He was moderately obese and acutely ill He was hiccuping and repeatedly had small watery emeses containing occult blood Temperature was 101 F pulse 120 blood pressure 160/76 white blood cell count 14 500 and amylase over 600 units

Broad spectrum antibiotics were started on the 3d hospital day because of protracted fever and continued for 21 days Intramuscular chloramphenicol 500 mg every 8 hours for 4 days was given then intravenous tetracycline 100 mg every 6 hours for 10 days then intramuscular chloramphenicol again 500 mg every 8 hours for 7 days

After 2 weeks of severe illness his condition gradually improved and he was asymptomatic by the end of the 3d week except for weakness and anorexia He was afebrile white blood cell count and serum amylase were normal Nasogastric suction and antibiotics were discontinued and hourly antacids and oral methscopolamine were begun

At the beginning of the 5th week temperature began to rise and reached 106 F Combined intramuscular chloramphenicol and intravenous erythromycin were given for 2 days Urine cultures showed large numbers of achromobacter A heavy growth of candida

(4) A.M A A h I t. Med 99 09 13 F b ry 19 7

was seen in 3 blood culture bottles and on blood pour plates there fore antibiotic treatment was changed to oral nystatin 1 500 000 units every 6 hours High temperature and general deterioration continued and the patient died 3½ days later

Autopsy showed 150 ml clear fluid in the abdomen the mid transverse colon adherent to the mesentery and an abscess cavity adjacent to the pancreas which contained pink fluid and necrotic tissue The cavity extended from the midpoint of the pancreas left



F g 3 — Ren l absc how g a d da Sch ff (Co rt y of B r tt B *et al* A M A. A ch I t Med 99 09 213 F bruary 1957)

to the hilum of the spleen Exterior and cut surfaces of both kidneys were studded with 1 2 mm hemorrhagic areas which contained candida (Fig 3) Scattered monilial abscesses were seen in the myocardium None were seen in the liver but it was edematous and contained infiltrations of leukocytes compatible with acute toxic damage Postmortem culture of the peripancreatic abscess grew C albicans and coliform bacteria Culture of the renal abscesses grew C albicans only

► [It seems questionable that the pancreatitis played a significant part in the pathogenesis of this generalized moniliasis The main thing is that a debilitated person was treated for many days with broad spectrum anti biotics In that connection it should be pointed out that pancreatitis alone uncomplicated by detectable bacterial infection can cause high fever for many days —Ed]

NEW KNOWLEDGE OF VIRAL DISEASES

Present Status of Etiologic Discovery in Viral Diseases Advances in the past 25 years are discussed by John F Enders[5] (Harvard Med School) Surprisingly many new viral agents responsible for human illness have been revealed Before 1910 only rabies poliomyelitis smallpox vaccinia cowpox yellow fever dengue and phlebotomus fever were known as viral diseases Between 1910 and 1919 measles varicella herpes zoster herpes simplex inclusion conjunctivitis and verrucae were added No additions were made between 1920 and 1929 but 1930 39 showed viral origins of St Louis Japanese B equines and Russian far east encephalitides influenza psittacosis lymphogranuloma infections mumps rubella lymphocytic choriomeningitis and Rift Valley fever Between 1940 and 1949 infectious hepatitis serum hepatitis Colorado tick fever and epidemic viral gastroenteritis were recognized During 1950 55 Coxsackie infections (pleurodynia herpangina meningitis myocarditis) APC RI ARD infections ECHO infections (meningitis) and Boston exanthem were found to be viral diseases

Continuing advances in knowledge of the etiology of viral infections is due to two factors A number of diseases with characteristics of an infection have been recognized only recently The second factor is methodology By 1914 each of the known means of virus cultivation—the living mature animal avian embryo and tissue culture—had been employed Advances since have been modifications and refinements of original methods

In 1949 poliomyelitis viruses were propagated in cultures of a variety of extraneural human tissues Degenerative changes regularly occurred in infected cells and provided a more rapid and convenient method of determining the presence of these agents than did animal inoculation Many viral species have cytopathogenicity when grown in susceptible cells By this method the infectivity of suspensions of the viruses can be measured and specific antibodies identified

(5) A I t M d 45 331 350 S pt b 1956

The first representatives of the Coxsackie family were demonstrated by inoculating fecal suspensions from patients with poliomyelitis symptoms into suckling mice The viruses are small about the size of poliovirus 30 mμ in diameter often found in the human gastrointestinal tract in health and disease and are of two groups A and B which produce different pathology in suckling mice At least 19 antigenic types are distinguished among group A strains and 5 among group B In cultures of human or monkey cells only four group A types are cytopathogenic while all those of group B cause cell degeneration They are known to cause aseptic meningitis epidemic pleurodynia and a highly fatal infant myocarditis sometimes accompanied by meningitis and encephalitis Coxsackie A viruses are less virulent than B in man and have been implicated in herp angina and several minor illnesses variously described as grippe influenza or summer diarrhea Connection with aseptic meningitis is probable but not established

Discovery of the Coxsackie family was followed in 2 years by recognition of the main members of another large group of viruses with certain common properties inhabiting the enteric tract of man They were originally designated orphan atypical or human enteric viruses and recently classified as the enteric cytopathogenic human orphan or ECHO group They are antigenically heterogeneous Already 14 antigenic types have been delineated and others will doubtless be added They do not cause disease in suckling mice or in any other animal species They are not related to other viruses in the human alimentary tract They are cytopathogenic for the cells of certain primates including man Relation to clinical disease in man is not yet apparent They do cause inapparent infection since antibodies specific for the strain of ECHO virus recovered have been shown in the same person Human gamma globulin contains neutralizing antibodies against several different types There is reason to believe that a number of cases diagnosed clinically as nonparalytic poliomyelitis are due to certain types of ECHO viruses

Members of the new and widespread group of respiratory tract disease viruses have been variously termed adenoidal

pharyngeal conjunctival respiratory infection and acute respiratory disease viruses Types 3, 4 and 7 cause the grippe like illness in recruits designated during the last war as undifferentiated acute respiratory disease Type 3 also may cause nonbacterial pharyngitis which occurs in children during summer and has been called pharyngoconjunctival fever Primary atypical pneumonia unassociated with cold agglutinins may also result from these agents

Giant cell pneumonia virus has been recovered in tissue culture from tracheal secretions and lung tissue from two fatal cases of the disease They induced cytopathic changes in renal epithelial cells indistinguishable from those of measles virus If the giant cell pneumonia virus is identical with that of measles then measles virus under certain conditions can produce disease clinically unrecognizable as rubeola

► [A fine condensation of recent advances in the field by one of the men responsible —Ed]

Recent Discoveries in Etiology of Acute Respiratory Infections Adenoviruses are reviewed by Robert Ward[6] (New York Univ) For many years the term virus has been loosely applied to miscellaneous respiratory and grippe like infections which behaved unlike bacterial infections Until recently the only respiratory viruses known were influenza A and B psittacosis and Q fever which accounted for only a few nonbacterial respiratory infections In the last 2 5 years a family of related viruses has been discovered Known as the APC AD ARD and RI viruses the name which has now been accepted is adenovirus They were first discovered when surgically removed adenoids from normal children were cultured in tissue

The virus was first called adenoid degenerating agent or AD agent There was no evidence that this virus was related to human disease but it appeared to be a latent virus unmasked by being separated from man and cultivated in tissue cultures Later several strains of cytopathogenic agents were isolated from soldiers with acute respiratory disease (ARD) a brief acute febrile infection with constitutional and local respiratory symptoms

In the summer of 1954 over 300 cases were studied in

(6) J P d t 49 480 484 O t b 1956

three outbreaks of an acute respiratory illness characterized by fever sore throat and conjunctivitis Most patients had headache and lassitude Fever lasted 5 or 6 days and cleared by lysis Sore throat was mild Physical findings were injection of the posterior pharyngeal wall which were studded with glairy lymph follicles nontender submaxillary lymph nodes and conjunctivitis Exudate was rarely purulent Classic antibody rises confirmed etiology

Recently another member of the adenovirus group type 7 has been isolated from throat washings in 44% of respiratory illnesses studied in a camp in California Types 4 and 7 appear to be the commonest adenoviruses associated with respiratory illness in military populations

Studies just begun indicate a relation between adenoviruses and certain acute respiratory infections in infants

The interval between isolation of new viruses and preparation of effective vaccines appears to be decreasing Discovery of adenoviruses is a salient advance but many problems remain So far no relation has been shown between the common cold and any adenovirus or other known virus

Structure and Development of Viruses Observed in Electron Microscope IV Viruses of RI APC Group Councilman Morgan Calderon Howe Harry M Rose and Dan H Moore[7] (Columbia Univ) describe the morphology as seen in infected cells of HeLa tissue culture of viruses of the respiratory illness adenoidal pharyngeal conjunctival (RI APC) group They propose a hypothesis concerning their manner of development and deduce the probable structure of the viral crystal

By electron microscopy irregular condensations of granular material are seen in nucleoli and scattered through the nucleus near them are clusters of spherical particles believed to be virus Some nuclei contain relatively large crystals (Fig 4) and a single crystal may occupy most of the nucleus Most viral particles show characteristic orientation but at the margins of the crystal they are randomly disposed

Many particles have a central body enclosed by a sharply defined membrane and average 24 mμ in diameter In Figure 5 four faces of a crystal traverse the corners of the field Swollen nuclei are repeatedly observed to have a cen

(7) J Biophys & Biochem. Cytol. 2 351 360 1956.



F g 4 —L g y tal w th p rt l d mly d t b t d t p pb y Lo l ed d f t n p rt l t y ent f eq t n u h ry t l d b l d a t f t N ru v bl n yt pl m d d f m ×16 000 (Court y f M g C t l J B phy & B och n Cyt l 351 360 1956)

tral region containing crystals and a peripheral zone in which the viral particles were dispersed at random (Fig 6) The peripheral zone is composed of fine granules and is less dense than the matrix of normal nuclei It resembles



F g 5—C y t l ffic ently m gn fi d t d t gu h lea ly tw type f p rticles—dense p rt l s w th pp t t rn l t t e d thos l d w th entral bod Th ar y th c y tal d t rt d tu d f om × 1 3 000 (Court sy of M g C t al J B phys & B och m Cyt l 351 360 1956)

the material in certain stages of development of herpes simplex virus

The viral particles vary in density and are approximately 60 mμ in diameter with a center to center spacing of about

F g 6 —N l w th t l on f den mat ix with l t r d ry tala f ru d per ph l f ʃ d mat l w th d pe d v ral p rt l ed d from ×15 500 (Court y f M g C f J J B ophy & B ochem Cyt l 2 351 360 1 56)

tral region containing crystals and a peripheral zone in which the viral particles were dispersed at random (Fig 6) The peripheral zone is composed of fine granules and is less dense than the matrix of normal nuclei It resembles



Fig 5—Cryst l s ffi ently magn fi d t d t g h le rly tw type of part cles—dense p rt l w th pp t t m l t t a d tho l d w th tral bod e Th r y th c y tal d t t d d d f m ×1 3 000 (Co rt y f Morgan C *et al* J B phys & B och m Cyt l 2 351 360 1956)

the material in certain stages of development of herpes simplex virus

The viral particles vary in density and are approximately 60 mμ in diameter with a center to center spacing of about

was a significantly rising titer in the neutralization test ECHO virus type 9 is a facultative neurotropic virus affect ing mainly the meninges and rarely causing paralysis The route of infection is air borne The disease has an incubation period of 5 15 days and is highly contagious affecting after exposure 50% of the family members and 80% of children and young adults

► [Not so many years ago an etiologic diagnosis could be made in only about 10% of cases of benign aseptic meningitis Now the figure is in the neighborhood of 30 40% —Ed]

Recovery of Virus from Cases of Epidemic Exanthema Associated with Meningitis For 5 summer and fall months an epidemic disease was observed in Sheffield England characterized by a rash and aseptic meningitis which at tacked many children under age 10 and more than one person in affected families Common initial clinical features at *onset of the illness were fever severe headache nausea and* vomiting The course was often diphasic and a child might be well from 1 5 days before fever and illness returned Many children showed a macular rash lasting a few hours or a few days usually of the cheeks and face although at times generalized It might be followed by local vesicula tion and scaling Of 6 patients with signs of meningitis all had pleocytosis and 4 had increased protein in the cerebro spinal fluid Cell counts were 50 1 584/cu mm mostly lymphocytes

D A J Tyrrell and B Snell[9] (Sheffield England) col lected nose and throat swabs in milk saline and feces for virus isolation Cytopathogenic changes similar to but less severe than those due to poliovirus occurred in culture The changes were transmissible and apparently due to a virus Neutralization tests revealed that the 16 strains of virus thus far isolated were the same Of 10 strains tested 9 caused paralysis in suckling mice The virus was not neu tralized by antiserums against poliovirus adenovirus types 1 11 and Coxsackie virus types A1 A10 and B1 B4 Neutral izing antibody was found in the serum of all 8 patients tested and a fourfold or greater rise was found in 5 of 6 paired serums

Cases resembling those in this epidemic have occurred

(9) La t 2 1028 1029 Nov 17 1956

65 mμ Many of the less dense particles exhibit an internal body averaging 24 mμ in diameter The viral particles are packed in a cubic body centered lattice

It is suggested that in the nucleus the virus differentiates from dense granular and reticular material and forms crystals Disintegration of crystals and disruption of the nuclear membrane releases virus into the cytoplasm No evidence suggests that the virus develops into cytoplasm

► [The electron microscope is beginning to open up a whole new world of knowledge in pathology as well as in physiology —Ed]

Disease Caused by ECHO Virus Type 9 Epidemiologic Clinical and Viroserologic Study is reported by Th Baumann M Barben R Marti A Hassler and U Krech[8] The epidemic caused by ECHO virus, type 9 affected 150 persons mostly children and young adults with about twice as many males The clinical picture was either abortive or fully developed The abortive form ran the course of an upper respiratory infection with slightly injected throat and conjunctivas temperature between 100 4 and 104 F which receded gradually or abruptly after 1 5 days severe frontal headache and occasional nausea or vomiting No other symptoms of central nervous system involvement such as nuchal rigidity or cerebrospinal fluid changes were observed Convalescence was short About 80% of the persons affected by the epidemic presented the abortive form of the disease

In the fully developed form a nonspecific initial phase was followed by benign subacute serous meningitis with nuchal rigidity Frontal headaches and retrobulbar pain were pronounced but subsided fast after lumbar puncture The cerebrospinal fluid cell count averaged 1 643/3 with only 28% lymphocytes The hemogram showed relative lymphopenia and slight shift to the left The sedimentation rate was high in the beginning Meningeal symptoms and fever lasted about 7 days on the average while convalescence took 3 5 weeks The cerebrospinal fluid became normal in about 1 month with increase in lymphocytes and without albuminocytologic dissociation

In 11 of 24 patients with meningitis ECHO virus type 9 was recovered from the stools In almost all instances there

(8) S hw med Wch sch 87 30 315 M 30 1957

7 years Bedjanic Rus Kmet and Vesenjak Zmijanac found that the disease typically presents two phases a prodromal and a principal phase separated by an afebrile latent period In 33% of patients prodromal symptoms pass unnoticed In others the disease develops gradually The first period appears to coincide with viremia which precedes the attack on the nervous system

Since the tick Ixodes ricinus is considered to be the principal vector the incubation period is the time from tick bite to first symptoms i e 4 days to 3 weeks usually about 10 days *Prodromal symptoms observed in 50% of* cases resemble grippe sometimes with meningeal signs (fever headache vomiting neck rigidity and more or less definite Amoss or Kernig signs) The sedimentation rate is not affected but leukopenia is typical in this stage After 2 5 days temperature decreases nerve symptoms disappear and the disease becomes latent for 4-20 days—in general 10 days The end of this period coincides with the end of leukopenia The principal phase then supervenes abruptly with high fever intense headache and continuous vomiting In 10% of cases there is loss of consciousness delirium or coma In benign cases meningeal symptoms are revealed only by careful examination

Cases in the 1953 epidemic presented for the first time encephalitic and encephalomyelitic characteristics similar to meningitis Nystagmus was present in 6 cases diplopia in 3 and vertigo anisocoria and urinary retention in others Six patients had temporary paralysis of the face 4 of the shoulder and 2 of the masticatory muscles Paralysis was flaccid without sensory involvement and appeared during the first days 75% of paralyses occurred in patients over age 30 At onset of the principal phase level of cerebrospinal fluid proteins increased Leukopenia of the initial and latent phases was replaced by neutrophilic leukocytosis (9 000 17 000 leukocytes 80 90% neutrophils) When fever subsided after about 8 10 days leukocytosis disappeared and leukopenia again occurred

So far no deaths have been reported but the disease may have caused some deaths attributed to acute encephalitis The patient s condition sometimes improves with amazing

( ) B ll W ld H lth O g 12 503 51 1955

in the Midlands and northern and eastern England The evidence suggests that this epidemic was caused by a virus related to Coxsackie group A

► [In Great Britain and continental Europe during recent years there were numerous epidemics of aseptic meningitis such as this one. Some seemed to be due to Coxsackie viruses some to ECHO viruses More serious disease occurred in central Europe the agent apparently being transmitted by tick bite and the clinical illness taking the form of encephalitis in many cases (See next three abstracts) —Ed]

Virus Meningoencephalitis in Slovenia —*I Epidemiologic observations* —J Kmet J Vesenjak Zmijanac M Bedjanic and S Rus[1] report on 208 hospitalized patients Since 1946 this meningitis of unknown origin originally called serous meningitis has been observed in Slovenia Studies begun in 1947 showed that it is endemic (with 90 9% of patients from rural regions) and has seasonal fluctuations (95% of cases from May to September with a maximum in July of 33% of total annual cases) The endemic zone is rural and forested in the center of Slovenia in 1953 when the disease became epidemic it extended northeast It has not been seen in other sections of Yugoslavia Cases have appeared simultaneously in several parts of the endemic zone Incidence in villages was sporadic (94.2% of cases) at intervals of weeks or sometimes months In 62% of cases tick bites undoubtedly originated the infection Young or middle aged persons were most frequently affected (56 2% aged 11 30) *No direct infection from man to man has been observed* and no hospital contagion has been reported It can be assumed that the disease existed in Slovenia before World War II but under a different name and that mortality was low

Epidemiologic clinical and virologic characteristics of epidemic meningoencephalitis resemble those of an encephalitis transmitted by ticks (Ixodes ricinus) described by Czechoslovakian authors and also the meningoencephalitis observed in western Russia and Austria The endemic rural character of this meningoencephalitis indicates that its natural reservoir may be wild rodents which are known carriers of the virus of Russian spring summer encephalitis Presence of enzootic foci is revealed from time to time by accidental infection in man

II Clinical observations —In a study of 500 patients over

(1) B II. Wo ld Health O gan. I 491 501 1955

the patient from whom virus was isolated Among 419 serums taken from patients in the acute or convalescent stage complement fixation tests with this antigen were specifically positive in 272 At a dilution of 1 2 190 serums were negative Some serums that were negative or showed a weak titer when inactivated at 64 C gave better results when inactivated at a lower temperature Optimal temperature for inactivation has not yet been established

Serums of patients with meningoencephalitis were all negative to Widal and Weil Felix tests to agglutination with leptospires and to complement fixation with agents causing grippe lymphocytic choriomeningitis Q fever and epidemic typhus Cross immunization tests by complement fixation with various strains of meningoencephalitic virus confirm that this Slovenian disease belongs to the meningoencephalitides

Virus Meningoencephalitis in Austria—*I Epidemiologic features* The epidemic which occurred in Styria Austria in 1953 was studied by Erika Richling[4] (Univ of Graz) in 304 patients hospitalized in Graz Hundreds of others were cared for in the provincial hospital The epidemic showed a seasonal periodicity with an increase of cases from June to September and a decline during the winter months maximum incidence occurred during the 29th and 30th weeks of the year The lowest proportion of paralyzed and encephalitic cases (20%) coincided with the peak of the epidemic This proportion increased to 48% in October and November and at the beginning of the outbreak Morbidity was greater in rural zones than in villages About 78% of patients came from rural usually wooded areas This was true also in other provinces of Austria Bohemia and Moravia About one third of patients reported tick bites and many others mosquito bites Only 16 patients (about 5%) were under age 10 and none of these died Maximal morbidity (48%) was observed in those aged 11 30 especially in males The proportion of paralytic cases increased with age except that it was high in children under age 10 (38%)

The virus is transmitted by several species of arthropods by ticks and probably by mosquitoes Transmission by dust or milk from infected goats is suggested by several familial

(4) B ll W ld H lth O gan 12 521 534 1955

rapidity Lumbar puncture relieves headache and vomiting Disappearance of fever marks further improvement Four weeks after onset of the meningeal phase most patients are convalescent but about 50% complain of malaise during this period The cerebrospinal fluid may remain abnormal for 8 months In the 1953 epidemic 4 patients had paralyses with muscular atrophy 8 months after the illness Paralysis of the shoulder region in 1 patient resembled that produced by Russian spring summer encephalomyelitis

Diphasic evolution a brusque change from leukopenia to neutrophilic leukocytosis and increased level of cerebrospinal fluid proteins are the principal diagnostic criteria Serologic diagnosis should confirm differentiation from poliomyelitis Tuberculous meningitis is sometimes difficult to exclude Experimental infection due to louping ill virus is indistinguishable from the final stage of Slovenian meningoencephalitis Russian spring summer encephalomyelitis has no prodromal stage and is clinically more serious with frequent permanent paralysis of the shoulder region The more benign European form of this disease resembles the Slovenian infection although the latter appears still milder

No antibiotic is effective against Slovenian meningoencephalitis Lumbar puncture has been the only symptomatic therapy

III Isolation of causative agent—Since 1947 many unsuccessful attempts were made to isolate the causal agent of Slovenian meningoencephalitis and in 1953 Vesenjak Zmijanac Bedjanic Rus and Kmet[3] successfully isolated the virus from the brain of a mouse inoculated with blood taken from a patient on the 6th day of the prodromal phase Seventeen passages of the virus were effected in white mice both adult and baby mice were susceptible to intracerebral and intraperitoneal inoculations Incubation was 4-8 days in mature and 3 or 4 days in baby mice The lethal effect of the virus on mice diminished with an increase in the number of passages No other isolation of the causal agent has been achieved Inoculation of minced Ixodes ricinus supposed to carry the virus into mice gave no positive results

Antigen prepared from mouse brain on the third passage showed complement fixation (titer 1 2 1 3) with serum of

(3) Bull. World Health Organ. 12 513 520 1955

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(4) B ll World Health O ga 12 5 1 534 1955

infections Overwork excessive exposure to sun trauma ill ness operations or pregnancy apparently are predisposing factors External factors may operate during the prodromal and latent periods to aggravate the course of the disease

Effective prophylaxis requires further knowledge concerning portals of entry and elimination of the virus duration of incubation and the natural reservoir of the virus

II Clinical features pathology and diagnosis—The same 304 cases formed the basis for a study by G Grinschgl[5] (Univ of Graz) Serious cases with paralytic or encephalitic manifestations comprised 26% of the total Like poliomyelitis the disease is most often diphasic The prodromal period lasts 2 8 days with symptoms resembling grippe The second phase after a latency of 8 12 days is characterized by virus invasion of the nervous system

During the epidemic of 1953 some patients (not included in the series) who displayed only influenza symptoms with normal cerebrospinal fluid and no involvement of the nervous system had antimeningoencephalitis antibodies in their serums revealed by complement fixation Hence it is assumed that as in poliomyelitis there are abortive cases in which the virus is not neurotropic The severity of disease is probably determined by the patient s ability to produce sufficient antibodies rapidly enough and by predisposing and aggravating factors

Autopsies revealed acute encephalitis especially with lesions of the gray matter Pathologic changes were particularly pronounced in the cervical medulla and the Purkinje layer in the cerebellum where cellular destruction was almost complete Involvement of the cerebellum was similar to that seen with louping ill and Russian spring summer encephalitis This is generally less marked in poliomyelitis but it is not a reliable differential criterion

Serologic tests were carried out for demonstration of antibodies by complement fixation and by neutralization 8% of cases were definitely negative and 76% definitely positive Possibly some negative results were obtained in patients with poliomyelitis since most of these were younger subjects with paralyses of the legs

It is extremely difficult in the isolated case to establish a

(5) B ll World Health O gan. 12 535 564 1955

differential diagnosis solely on clinical and pathologic cri teria However the large number of cases studied during the Austrian epidemic permits certain conclusions valid dur ing an epidemic Meningoencephalitis with manifestations of spinal paralysis radiculitis and transverse myelitis greatly resembles Russian spring summer encephalitis but is less severe In both diseases shoulders and arms are preferen tially attacked by paralysis Compared with poliomyelitis meningoencephalitis more often presents a prodromal peri od and its latent period is generally longer In this epidemic 74% of cases showed only meningitis this group does not exceed 50% in poliomyelitis Paralytic cases are less frequent than in poliomyelitis and fatalities (14 cases—4 6% in this series) are fewer The sedimentation rate is greatly increased in meningoencephalitis in contrast with poliomyelitis No specific treatment of virus meningoencephalitis has been dis covered

III Pathogenic and immunologic properties of the virus —Four strains isolated from central nervous sytems of pa tients who died during the epidemic were studied by J D Verlinde H A E van Tongeren S R Pattyn and A Rosen zweig[6] (Netherlands Inst for Preventive Med Leiden) One was recognized as a strain of poliomyelitis type I The other strains Graz I II and III produced clinical and path ologic signs of encephalomyelitis in monkeys and mice In oculation of chick embryos produced lesions and caused ede ma and icterus with death in 5 6 days Necrotic foci were found in the liver and cardiac muscle Susceptible animals were infected by the intracerebral intraperitoneal intramus cular subcutaneous or intranasal route Receptive hosts modes of experimental infection and clinical and histologic characteristics of the experimental disease were similar to other encephalitides transmitted by arthropods The geo graphic localization of the epidemic suggested a relation with Russian spring summer encephalitis or a strain of loup ing ill (infectious encephalomyelitis of sheep)

Neutralization of virus by specific immune serums showed that Graz I and II strains were identical Besides homolo gous strains Graz immune serum neutralized more or less completely Russian spring summer encephalitis a strain

(6) B ll W ld H lth O g 12 565 579 1955

of meningoencephalitis of Slovenia (1943) and the Stilleroba strain of Czech encephalitis (1948) Cross neutralization tests revealed slight immunologic differences between Graz Stilleroba and Russian spring summer encephalitis Tests on serums of convalescent patients showed an immunologic re lation between Graz and Russian spring summer encepha litis viruses

IV Viremia in experimental infection attempts at trans mission by mosquitoes—S R Pattyn and R Wyler[7] (Neth erlands Inst for Preventive Med Leiden) attempted experi mental infection with the Graz I strain using the 7th mouse brain passage the LD_{50} of which for mice was 0 02 ml of 10^{-5} dilution No virus could be demonstrated in the blood of rats up to 6 days after subcutaneous inoculation of 0 1 ml of 10^{-1} 10^{-3} dilutions or in the blood of ducks or pigeons up to 15 days after inoculation Virus could be demonstrated in rabbits for 3-4 days after inoculation with 1 2 77 mouse LD_{50}/Gm body weight in chicks for 8 10 days and in hens and sparrows for 4 7 days

Attempts to transmit the disease by bites of mosquitoes engorged on infected animals were unsuccessful Virus could be demonstrated in Culex molestus for only 18 24 hours after engorgement and for 5 6 days in Anopheles maculipennis var atroparvus Other experiments on chicks indicated the *virus may multiply at the site of inoculation and in the retic* uloendothelial system

It was concluded that the animals studied were not im portant in spread of virus meningoencephalitis in Austria although the rabbit and hen may constitute a dangerous temporary reservoir Retention of virus in sparrow s blood for a considerable time raises the question of the role of ecto parasites and migrations of birds in the epidemiology Al though C molestus did not appear to be significant in spread ing of the disease A maculipennis may play a secondary role

Serologic Aspects of Virus Meningoencephalitis Study of Reactions of Two Viruses Isolated during 1953 Epidemics in Slovenia and Austria is reported by William L Pond and Sudie B Russ[8] (Army Med Service Grad School Wash

(7) B ll World H lth O ga 12 581 589 1955
(8) Ib d. pp 591 594

ington D C) The two strains of virus were designated Slovenia and Graz

Information received from Yugoslavia indicated that the clinical and epidemiologic manifestations of the Slovenia epidemic differed from epidemics in western Russia and Czechoslovakia caused by the Russian spring summer encephalitis virus and that of louping ill The Slovenia and Graz strains were compared by intracerebral neutralization tests to strains of other viruses including Japanese encephalitis B West Nile St Louis Murray Valley eastern and western equine American encephalomyelitis and Russian spring summer encephalitis No relation was demonstrated to any but anti Russian spring summer encephalitis serums (four strains from different sources) anti louping ill and Czech antiencephalitis reactions with these were practically identical The Slovenia and Graz strains evidently belong to this group of encephalitis viruses

Association of New Type of Cytopathogenic Myxovirus with Infantile Croup Most infectious croup in infancy seems unrelated to Corynebacterium diphtheriae or Hemophilus influenzae B and other pathogenic bacteria have not been implicated The term viral croup has been applied although an etiologically associated virus had not been identified Robert M Chanock[9] (Univ of Cincinnati) isolated two viruses which produced an unusual spongelike cytopathogenic effect in tissue culture of monkey kidney epithelium The viruses were isolated from pharyngeal swabs of 2 of 12 infants with croup These infants and 3 other patients developed significant increases in neutralizing or hemagglutination inhibition and complement fixing or all three varieties of antibodies during convalescence The isolated agents appeared similar antigenically

The properties of the virus were consistent with those required for classification in the myxovirus group No antigenic relations with influenza A A B and C Newcastle or Sendai viruses were found The viruses were distinct from mumps virus but the existence of a common antigen was suggested

The high incidence of infection with this new virus in one group of croup patients suggests it may be at least one etio

(9) J E p M d 104 555 576 O t 1 1956

logic agent of this clinical syndrome but more extensive control studies are needed to prove specific causal association

Acute Aseptic Myocarditis and Meningoencephalitis in the Newborn Child Infected with Coxsackie Virus Group B, Type 3 A case is reported by Sidney Kibrick and Kurt Benirschke[1] (Harvard Med School) The etiologic role of certain coxsackie viruses in various human illnesses is now established Group B strains can cause aseptic meningitis and encephalitis

Pleurodynia is caused by these agents Group B viruses have also been reported associated with many clinical dis eases including acute febrile illnesses either uncomplicated or resembling influenza infectious mononucleosis sinusitis and appendicitis In the case reported the mother s infection just before delivery was probably a nonspecific manifesta tion of infection with Coxsackie virus Delivery by cesarean section and development of signs of illness shortly after birth despite absence of further contact with the mother clearly imply intrauterine infection

Certain cases of acute myocarditis not due to larger micro organisms are at present considered a form of primary myo cardial disease some of these may be caused by viruses

Woman 37 para III gravida IV had an upper respiratory in fection with coryza sneezing and malaise during the 38th week of gestation Two days later she passed a large amount of blood per vaginam Diagnosis of placenta previa was made and immediate cesarean section performed

The infant breathed spontaneously and appeared well but several hours later she had a croupy cough when she cried and an inspira tory crow On the 3d day the temperature (rectal) rose to 100 2 F A chest film showed bilateral atelectasis without evidence of pneu monitis Lumbar puncture revealed a clear xanthochromic cere brospinal fluid under normal pressure with a 2+ Pandy reaction negative test for sugar and 132 white cells/cu mm of which 95% were mononuclears Another lumbar puncture the same day showed similar findings but the next day the 6th the condition became worse and lumbar puncture showed 327 white cells/cu mm She died on the 7th day

At autopsy diffuse myocarditis was found chiefly near the annulus fibrosus consisting of infiltration with polymorphonuclear leukocytes macrophages and occasional lymphocytes The meninges were edem atous and diffusely infiltrated with moderate numbers of macro phages and occasional polymorphonuclear leukocytes The spinal

(1) New England J Med 255 883 889 No 8 1956

cord showed degenerative and inflammatory lesions in the lateral aspects of the anterior horns and in the reticular formations

A section of thoracic spinal cord was inoculated as a suspension into cultures of human renal tissue and human embryonic skin and muscle A transmissible cytopathogenic agent was cultured in the renal tissue and identified as Coxsackie virus group B

POLIOMYELITIS

Pathogenesis of Poliomyelitis is discussed by Frank Fenner[2] (Australian Nat l Univ) Attempts at immunization can be understood only in terms of the modern concept of pathogenesis

The portal of entry of the virus is not the exposed ends of the olfactory nerves as once thought but the gastrointestinal tract Apparently in both ape and man there are susceptible cells in the tonsillar pharyngeal region and small intestine which are invaded first Large amounts of virus are liberated from these cells into the lumen of the gut and excreted in the feces for as long as 4 months These intestinal infections are of no clinical interest but can induce production of specific antibody and persons so affected can widely disseminate the virus

If poliomyelitis virus caused nothing more than this asymptomatic condition it would be relatively unimportant but it occasionally infects cells of the human nervous system It is not confined to nervous pathways Like all generalized viral infections there is a blood stream phase—a stage of viremia which may often occur in the early stages of abortive and nonparalytic poliomyelitis as well as in the paralytic disease (Most infections in nonimmune persons are associated with viremia whereas infections in the alimentary tract occur principally in persons with circulating specific antibody)

It is rare for the virus to locate in cells of the nervous system after viremia and there is scanty information on the mode of passage of virus from the blood to cells of the central nervous system The variations in penetrability of blood vessels in the region of the central nervous system is of critical importance Cortisone in animals profoundly modi

(2) M J A t 1 1 203 08 Feb 11 1956

fies resistance to intracerebral and intraperitoneal inoculation of poliomyelitis virus Different strains in each serologic type of poliomyelitis virus vary markedly in ability to invade the central nervous system

Differential Diagnosis of Acute Poliomyelitis Four Year Study of 717 Cases of Suspect Poliomyelitis in none of which was the disease present is reviewed by T C Papermaster[3] (Elizabeth Kenny Inst Minneapolis) It was believed that listing the diseases in this series would make a field study of the differential diagnosis During this same period 2 275 other patients had acute poliomyelitis a ratio of 3 1

During many months of the year more nonpoliomyelitis than poliomyelitis cases were seen Respiratory disease comprised 37 7% of the 717 cases including influenza 'flu like illness and nonspecific upper respiratory infection in the terms of the referring physicians who replied to a questionnaire In about 46 cases (6 5%) orthopedic disabilities mostly limb or back pain were present and in 154 (21 5%) neurologic disorders

Many syndromes and diseases simulate poliomyelitis but it is absurd to confuse certain entities with poliomyelitis Careful history and physical examination will often prevent unnecessary hospitalization However in almost every instance there was some justification for suspicion of poliomyelitis

The important lesson is that early poliomyelitis with borderline findings may be indistinguishable from many diseases If poliomyelitis can confound experts until the virus is grown from stool cultures or sufficient time has elapsed for serologic data to be obtained it is reasonable that the average practitioner may be unable to differentiate the diagnosis during the initial examination It may be convenient and desirable to seek help from a center

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Poliomyelitis in Greenland is reviewed by Mogens Fog Poulsen[4] All Greenland is north of the 10 degree isotherm and has a polar climate The southern areas have average

(3) M[illegible]esota [illegible] 59 364 J[illegible]e 1956
(4) Da[illegible] b[illegible] 46 December 1955

temperatures above zero the northernmost inhabited portion an average of —10 C There are neither roads nor railways and all traffic is by boat or sledge Density of population is 0 07 inhabitant/sq km of ice free territory and the inhabited places are all close to the sea

Some towns have sanitary regulations but in most they are not effective There is no actual system of removal of refuse and night soil Few private houses have lavatories very few have drains There are few public lavatories Water is generally obtained from wells or small lakes and brooks commonly contaminated Because of the low temperature the earth has slight purifying properties

During the past 100 years poliomyelitis has occurred repeatedly in characteristic epidemics In this century there have been at least 4 epidemics Actual sporadic cases of poliomyelitis are most rare Outbreaks could be connected with foreign navigation though contagion must have been conveyed by healthy persons The epidemics were most frequent during late summer presumably due to transmission by crews of foreign ships The epidemics passed quickly in the separate districts In small settlements an epidemic generally lasted about 10 days Most frequently about a year passed from transmission of infection to cessation of the disease Morbidity was apparently almost universal in the age groups born after the previous epidemic Mortality was 0-4% of the population in districts attacked

Poliomyelitis Vaccination in Fall of 1956 is reviewed by Jonas E Salk[5] (Univ of Pittsburgh) Interest centers around the question as to whether effective durable immunity to virus disease is acquired only through infection or whether it can be induced by a nonliving antigen Whether a killed virus vaccine properly prepared and used prevents paralysis of poliomyelitis will soon be known

There is agreement that the virus reaches the central nervous system via the blood stream and that virus neutralizing antibody in the circulating blood effectively intercepts virus invasion of the central nervous system There are indications that antibody is not only effective in preventing paralysis if present in the blood at time of exposure to natural infection but that sometimes antibody can effectively reappear

(5) Am J P b Health 47 1 18 J ry 1957

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(5) Am J P b He lth 47 1 18 J y 1957

through a hyperreactive immunologic mechanism primed by the earlier immunologic experience and later set off by exposure to the living virus in nature Thus where antibody concentrations after infection or vaccination have declined to nondetectable levels invasion of the central nervous system can still be prevented although infection of more superficial tissues is not

Speed and degree of antibody response to vaccination are considerably increased in persons previously sensitized by infection or vaccination An antibody rise is evident in 3-4 days Higher levels of antibody have been observed after natural infection in persons previously vaccinated compared with those not vaccinated This suggests that previously vaccinated persons hyperreact immunologically when exposed to natural infections Even a single dose of vaccine of adequate potency could induce long lasting immunity It would not be wise to rely on but 1 dose of vaccine The immunologic effect of 2 doses spaced over several weeks is greater than that of a double dose given at once and chance of failure of a 1 dose procedure due to vaccine of relatively low potency or to low responsiveness of certain persons would be minimized *A combination of adequate dosage and lapse of sufficient time can give immunity equal to or greater than that of natural infection* The hyperreactive state induced by administration of killed virus vaccine might be as effective for immunity as that of natural infection

The intradermal route does not increase efficiency of response sufficiently if at all to permit reduction in quantity of vaccine administered without sacrifice of effectiveness for persons who require more than minimal quantities of vaccine for response

A year ago emphasis was principally on technical details concerned with production of a safe vaccine This year emphasis is on effectiveness or potency The first factor is growth of virus in a tissue culture system that will yield in a unit volume of fluid a sufficient concentration of antigen The second important factor is filtration crucial for safety which must be done so as to lose little or no antigen This has been solved on a manufacturing scale by adoption of uniform filtration methods employing the Seitz filter and by suitably balancing the volume of fluid processed against the

tendency of the filter to adsorb and to release virus The third factor concerns the possibility of destruction of antigenicity by overinactivation or by the effect of a preservative for sterility

All children who were vaccinated in the 1954 field trial should be revaccinated because much of vaccine used then was poorly antigenic and intervals between inoculations too short Some of these children have not yet been revaccinated and have a false sense of security Those children who were given 0 1 ml intradermally should also be revaccinated Some children received 3 doses in 5 weeks Additional in oculations should be considered giving the benefit of any doubt to the child so treated

Time is yet too short to evaluate protection against para lytic poliomyelitis afforded by 3 doses of vaccine as presently prepared and administered Until this is known recommen dations cannot be made about further inoculations Three injections of 1 ml each should be given to all potentially susceptible persons In the United States paralytic polio myelitis has occurred in persons in the 6th and 7th decades of life although such cases are rare However it is not un usual for persons in the 3d 4th and 5th decades to be severely stricken In recent years about a quarter of the total inci dence has been in this age group

Vaccination against poliomyeliti should be added to pro cedures now employed for the prevention of diphtheria tet anus and pertussis Whether it will be necessary to reinocu late later in childhood at the age of entrance into school or later will be answered more readily in the future

Poliomyelitis and Prophylactic Inoculation Against Diphtheria Whooping Cough and Smallpox A causal rela tion has been suggested between paralytic poliomyelitis and inoculation of prophylactics against diphtheria and whoop ing cough given alone or mixed Medical health officers in England and Wales collaborated with the Medical Research Council Committee on Inoculation Procedures and Neuro logical Lesions[6] in a study of this problem

Between 1951 and 1953 all cases of paralytic poliomyelitis in children in England and Wales were investigated in which the patients had had an injection of diphtheria or whooping

(6) La et 2 1 23 1231 Dec 15 1956

cough prophylactic or smallpox vaccine within 12 weeks before onset of symptoms Altogether 355 cases were investigated *Of 222* cases *in children who had completed a primary* course of inoculations or had been given reinforcing doses 132 developed paralysis 1 28 days after inoculation mostly around days 11 and 17

An estimated 1 in 37 000 inoculations precipitated paralytic poliomyelitis Risk did not extend beyond about 1 month after inoculation A series of inoculations had no cumulative effect Risk was greatest with alum precipitated diphtheria pertussis and least with toxoid antitoxin floccules and formol (diphtheria) toxoid Alum precipitated toxoid purified diphtheria toxoid aluminum phosphate precipitated and mixed nonalum precipitated prophylactics were intermediate Plain pertussis vaccine appeared relatively safe Smallpox vaccine evidently did not provoke poliomyelitis

About 13% of paralytic cases in children aged 6 months to 2 years in county boroughs and large urban areas were causally related to inoculation This represents about 170 cases between 1951 and 1953 In children about age 5 the age when reinforcing doses are usually given cases provoked by inoculation probably formed only 2% of the total The period of highest risk was the 2d quarter of the year

A clear relation between site of inoculation and site of paralysis was demonstrated Those inoculated subcutaneously *were as likely to develop paralysis as those inoculated* intramuscularly There was no evidence of virus transfer via syringes

The mechanism by which inoculation acts is still unknown However it genuinely predisposes to paralysis and does not act merely as is sometimes supposed by determining the site of paralysis The risk involved in use of different vaccines and toxoids, seasonal variation in risk and the apparent similarity in risk between subcutaneous or intramuscular injection raise practical problems which must be considered in inoculation of children with whooping cough vaccines and diphtheria toxoids singly or in combination

Properties of an Ideal Poliomyelitis Vaccine are documented by John R Paul[7] (Yale Univ) Natural immunity reactions in poliomyelitis are guides in planning artificial

(7) Bull New York Acad Med. 32 747 752 October 1956

immunization In the United States there is a delayed proc ess of natural infection and immunization against clinical poliomyelitis Most adults do not become immune to one two or occasionally all three types of poliomyelitis virus until they are at least aged 25 Elsewhere the process may be much faster and more thorough with immunity in the early years of life This must have been the method 50 75 years ago when poliomyelitis was an infantile disease But today such populations of young children heavily immu nized naturally are found only where sanitation is primitive

In North African communities 90 100% of children are born with neutralizing antibodies to several types of polio myelitis viruses by transplacental passage from the mother These passive antibodies are lost in the first 6 months of life and active infection is almost immediately acquired At age 2-4 years 50% of children have antibodies to all three types and at age 5 9 years 80% In this population by age 10 12 natural immunity is solid against reinfection by any type of poliomyelitis Acute paralytic poliomyelitis is limited to the youngest ages Adult poliomyelitis is practically unknown and large epidemics as in the United States and Scandinavia do not occur

However infants acquire their immunity at the price of infantile paralysis Circumstances which disseminate polio myelitis viruses through the community and infect infants are those which spread agents of enteric infections result ing in high rates of typhoid fever and infant mortality In the United States exposure and infection are suppressed in early life Antibodies and immunity in all three types of poli omyelitis viruses are not acquired by most children until early adulthood With so many susceptible in the popula tions epidemics are common Paralytic and nonparalytic cases in adults have increased steadily since 1900

The goal for artificial immunization therefore is to pro duce quickly during infancy the same solid lasting immu nity without paying the natural price of the occasional para lytic case and without trusting to primitive sanitation to provide early exposure to the viruses The highest ideal of artificial immunity is a vaccine of remarkable potency of which one course of inoculations renders solid immunity against reinfection for life The next most ideal vaccine

might prevent paralysis but not necessarily infection On this basis the idealist s choice of a vaccine might be a live (attenuated and avirulent) virus used naturally as an im munizing agent by feeding to infants at age 6 months or less without presuming that one feeding would suffice to protect against paralysis for life But one feeding might pro tect against paralysis for some years Subsequent natural in fections or refeeding the vaccine might provide the nec essary booster infections It may not be a question of de ciding between a dead or live virus vaccine but accepting a combination of both

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VARICELLA

Varicella Report of Two Fatal Cases with Necropsy Vi rus Isolation and Serologic Studies is presented by William J Cheatham Thomas H Weller T F Dolan Jr and John C Dower[8] (Boston)

CASE 1—Boy 4 while being treated with 4 amino N 10 methyl pteroylglutamic acid for disseminated neuroblastoma developed vari cella with vesicles continuing to appear for 17 days The inflamma tory response was diminished and the eruption was zosteriform He showed evidence of viral infection of multiple dorsal root ganglions and the myenteric plexus of the small intestine Virus was isolated from the blood vesicle fluid and lung by tissue culture Despite the duration of the disease demonstrable specific complement fixing antibodies did not appear

CASE 2—Girl 7 had acute rheumatic fever with active carditis for which she was receiving cortisone She had had this therapy 4 weeks when 18 days after exposure a varicella rash developed on the trunk back and face The course was fulminating with hyper tension coma convulsions cyanosis and muscular twitchings Death occurred 4 days after the rash appeared At autopsy widespread vascular damage and hemorrhage were seen Varicella virus was recovered from the blood and vesicle fluid

Autopsy findings resembled those in previous fatal cases of varicella with focal necrotic areas frequently containing type A intranuclear inclusions in the skin liver lungs spleen adrenals gastrointestinal tract and pancreas Intra nuclear inclusions in vascular endothelium is noted early in the evolution of the lesions Morphologic differentiation from lesions of herpes zoster is impossible

(8) Am J P th 3 1015 1035 Sept -O t 1956

Usually complement fixing antibody appears about the 5th day of illness and rapidly increases to high levels In Case 1 this did not occur and vesicles continued to develop At death virus was recovered from the blood At autopsy the characteristic cellular inflammatory response was not seen in the necrotic lesion Determinations showed no hypogam maglobulinemia The significance of treatment with radia tion and methotrexate is obscure

The striking morphologic feature of Case 2 was the sever ity of vascular damage with edema and widespread hemor rhage There is sufficient evidence to suggest that the corti sone used in treating the rheumatic fever may have unfavor ably influenced the course of the varicella A second rapidly fatal case of varicella occurred during cortisone treatment

► [The evidence that preceding cortisone therapy may have been respon sible for the fulminating course of the 2 cases mentioned is to be noted. However cortisone therapy has been employed in treatment of some cases of varicella pneumonia without apparent harm The difference may be in the time sequence i e the fatalities mentioned here were in patients who developed varicella while already under the effects of cortisone.—Ed]

Primary Chickenpox Pneumonia has a characteristic roentgen appearance according to Diana Y M Tan S A Kaufman and George Levene[9] (Boston) It was a complica tion of chickenpox in 16 cases all but 1 in adults Onset of respiratory symptoms occurred within five days of the rash which in all cases was severe and confluent over the whole body Vesicles were found in the mouth and pharynx. The patients were acutely ill with temperatures of 101 105 F and severe cough several developed hemoptysis and half had chest pain and dyspnea Physical examination of the chest was not remarkable despite extensive roentgen changes Lung pathology was similar to that of other viral pneumonitides swelling proliferation and desquamation of alveolar septal cells and a predominantly mononuclear cell infiltration Bacteria were rarely seen foci of necrosis and hemorrhage were present

Roentgen findings in all cases were similar and character istic There were widespread nodular densities superimposed on markedly increased bronchovascular markings (Fig 7) In a few cases nodules tended to coalesce to simulate patchy areas of consolidation Roentgen evidence of infiltration per

(9) Am. J Roentgen 1. 76 527 532 September 1956

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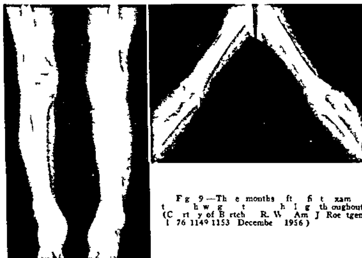
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F g 8 —Symmet cal l ment of k s lbows l g f m nd arms about m th afte t f l (Court y of Bertche R. W Am J Roe tgen ol. 76 1149 1153 Dec mbe 1956)



F g 9 —Th e months ft fi t xam t h w g t h l g th oughout. (C rt y of B rtch R. W Am J Roe tgen l 76 1149 1153 Decembe 1956)



F g 7—Cl e up of m dlu g field sh wing nod l a d g eral ed ease in broncho a cular m kings (Courtesy of Ta D Y M et l Am J Roe tge ol 76 527 532 S ptember 1956)

sisted 3 18 days with an average of 9 days As pneumonia regressed the infiltrates faded without any definite pattern of resolution The disease usually runs a relatively short course

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VARIOLA

Osteomyelitis Variolosa specific involvement of bone in smallpox has been described pathologically clinically and roentgenologically Robert W Bertcher[1] (New York) followed the early course of this complication in many children in Korea X rays were taken at a U S Army Station hospital

In all cases attention was first drawn to the elbow or knee No other joint was involved Mild swelling of the para articular soft tissues was usual Involvement appeared uni

(1) Am J Roe tgenol 76 1149 1153 D c mbe 1956



F g 8—Symmetri l l ment f k lbow l g f earm d arms bout month ft o et f va ola (Court y f B rt h R. W Am. J Roe tgen l. 76 1149 1153 Dec mbe 1956)

F g 9—Th m th ft fi t xamin t on h w g t e h l g th oughout. (Court y of B rtch R W Am J Roe tgen l. 76 1149 1153 Dec mbe 1956)

lateral clinically, but x ray examination revealed the disease to be bilateral in all cases As a rule all portions of a bone were affected with destructive changes and numerous irregular areas of bone resorption (Fig 8) Three month follow up studies showed extensive bony regeneration in areas of *previous destruction (Fig 9)*

Healing occurred despite malnutrition and intercurrent infections In some cases casts were applied to limit motion at an affected joint in the hope that permanent deformity could be avoided their value was inconclusive

Epidemic of Smallpox at Vannes from December 1954 to March 1955 is described by Leroux Amphous Billaud Bouillaud G Cadoret Delord Y Duhamel Lobrichon Baldrich and Audouy[2] Except for a few localized outbreaks in the last 15 years smallpox has been rare in France for 50 years because of compulsory vaccination Certain circumstances seem to favor renewed activity of the virus movements of populations social changes rapidity of air transportation endemic or epidemic variola in Africa or Indochina and negligence in rigid insistence on revaccinations and even first vaccinations

Two circumstances extended the epidemic at Vannes and confined it to hospital population Because of failure properly to diagnose the first case the child aged 2 was admitted to the pediatrics service where 8 other children and 1 employee were infected Lack of isolation of doubtful cases on the contagious ward which occupied the same wing as a general medical service of 40 beds also contributed When the first children with smallpox were transferred into the contagious ward the whole pavillion was contaminated and 38 patients undergoing medical treatment were exposed As soon as the nature of the outbreak was recognized rigorous prophylactic measures (systematic vaccination of patients and hospital personnel and careful epidemiologic investigations) must have limited the epidemic which was confined strictly to the hospital

Of 73 patients who contracted smallpox 56 were hospital patients the other 17 had professional or other contact with them The first child whose illness was not correctly diag

(2) Presse méd 63 639 642 Apr 30 1955

nosed was admitted Dec 9 1954 Later study indicated that he had probably been infected by a garment brought him by his father recently repatriated from Indochina Affected patients in the second and third waves of the epidemic included 16 children being treated in the hospital 30 of 38 adults hospitalized on the medical service 6 hospital employees 4 doctors 6 aged patients from an adjoining general hospital 9 patients (2 children) whose infection resulted from fortuitous contacts and 1 isolated patient in whom the origin of infection could not be traced A few sporadic cases were observed in a fourth wave Jan 20 Mar 1 1955 All but 5 patients (all children) were infected directly

Twenty three cases were of moderate or average severity 12 in children and 11 in adults Four of the latter died because smallpox aggravated pre existing disease Nine cases (5 in children) were virulent and rapidly lethal Among 41 mild or abortive cases 3 deaths occurred because of aggravation of previous disease Although existence of previous infection did not necessarily cause a virulent type of smallpox high mortality was partly dependent on previous disease in certain patients Five children who died were convalescing from recent infections Of 11 adults who died 4 were aged with senile cardiopathy or hepatitis

In 25 cases there was no eruption but the patients had a generalized illness which developed 10 or 11 days after exposure to smallpox In 16 the illness was only febrile and in 9 the general infectious syndrome was accompanied by more or less pronounced respiratory symptoms with labile infiltrative radiologic changes X ray findings were similar in 5 of 12 patients with mild eruptions Presumably these pulmonary lesions were related to variolar infection There was no evidence that noneruptive cases febrile or pulmonary were contagious

Findings in this epidemic emphasized the importance of vaccination Of 18 children 15 aged 5 months to 9 years had never been vaccinated 5 of these died Revaccination a short time before exposure did not always confer immunity but in general seemed to attenuate the infection

Family Epidemic of Psittacosis with Occurrence of a Fatal Case is reported by Robert L Prouty and William S Jordan, Jr [3] (Western Reserve Univ) The import and sale of psittacine birds has much increased since the relaxation in 1951 of federal regulations governing their quarantine and shipment Human psittacosis has shown coincident sharp increase

Parakeets and parrots are the principal source of human infection although the disease can result from contact with other birds The virus may be disseminated by an apparently healthy bird a fact often overlooked by the physician and unknown to the layman

The affected family a Negro minister his wife and 10 children (4 boys and 6 girls) aged 2 18 years had purchased 2 parakeets at a dime store The birds were in their home only 2 weeks and appeared in good health They ate and drank well, sang normally had smooth feathers and did not sneeze The parents became ill first developing symptoms about 11 days after their last contact with the parakeets and symptoms appeared in the eldest daughter the next day The parakeets were the source of the infection in all members Person to person spread did not occur

Man 40 had increasing malaise weakness chills fever headache and occasional nausea and vomiting for 12 days A slight nonproductive cough began 2 days before admission He was acutely ill with a dry cough and shallow rapid respirations Rectal temperature was 100 2 F and pulse rate 108 He had percussion dulness over the posterior right chest and entire left lung with bronchial breath sounds and many coarse inspiratory and expiratory rales The remainder of the physical examination was normal The leukocyte count was 64 000 He continued in coma had extreme respiratory distress and died 6 hours after admission

The parakeets had been purchased from a store which usually sold 100 150 birds a month The month before 100 birds were received by the store and 15 died an unusually high number The salesgirl caring for the birds added oxytetracycline to the drinking water of the sick birds until they either recovered or died This is a particularly pernicious practice since it fails to eliminate infection in a number of birds and

(3) A M A. Arch I t Med 98 365 371 September 1956

converts them to asymptomatic carriers constituting an ever present source of human infection in the home

At the time of investigation the store had 15 parakeets Because 2 months had passed since the purchase by the family it was unlikely that any birds of the same lot were left However 3 parakeets were tested and psittacosis virus recovered from 1 Blood from 10 employees of the store revealed elevated complement fixing antibodies in 2 salesgirls who handled birds regularly

The increasing number of human cases of psittacosis although many represent occupational infections traceable to nonpsittacine birds calls for reconsideration of control measures The most dangerous source is still the parakeet in the home Persons acquiring these pets should be informed that seemingly healthy birds may disseminate virus and bring sickness and even death to the family

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HERPES ZOSTER

Visceral Lesions in Herpes Zoster The peripheral nerves and posterior and trigeminal sensory nerve roots contain not only various sizes of myelinated but also unmyelinated afferent fibers Distally the afferent unmyelinated fibers originate (or end) as free nerve endings in the epidermis dermis and deeper tissues including muscles Unmyelinated afferent fibers with their cell bodies in the posterior root ganglions run from the viscera uninterruptedly through the autonomic ganglions and white rami communicantes to enter the posterior nerve roots with those from somatic tissues R Wyburn Mason[4] presents 8 cases and a review of the literature on herpes zoster

Irritation of the unmyelinated afferent fibers in the posterior nerve roots or peripheral nerves or their cell bodies in the posterior root ganglions may be expected to produce changes not only in the skin and somatic tissues but also in the viscera Some localized visceral disturbances have been seen with the skin lesions e g tachycardia pleuritic pain friction rub or pleural effusion gastrointestinal disturbances disturbed passage of food down the esophagus ab

(4) B t. M J 1 678 681 M 23 1957

dominal colic spasm of the prepyloric region of the stomach hematemesis persistent hematuria inflammatory changes in bladder mucosa hemorrhagic cystitis and rectal disturbance

Visceral disturbance in patients with herpes zoster occurs particularly in those viscera or parts of viscera supplied with afferent fibers by the posterior nerve roots corresponding to the zonal skin areas affected Accompanying the segmental skin lesions there are disturbances in the viscus or part of the viscus innervated by the corresponding nerve roots which cause inflammatory lesions and spasm of the hollow organs

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INFECTIOUS MONONUCLEOSIS

Palatine Petechiae an Early Sign in Infectious Mononucleosis Charles B Shiver Jr Perry Berg and Eugene P Frenkel[5] (M C U S A F) collected a total of 39 patients with mononucleosis and found 21 with stippled petechial hemorrhages in the soft palate In some cases the diagnosis was suspected primarily because of this eruption and in others it was a helpful sign

The eruption consists of multiple pinpoint petechiae on the soft palate usually near the junction with the hard palate but sometimes near the midline more posteriorly on the soft palate Sometimes sparse petechiae were seen on the hard palate also One patient had some on the uvula No patient had associated petechiae on the skin or in other parts of the oral cavity The petechiae varied from 10 to several hundred in number lasted 3 11 days and then faded completely leaving no trace

Eleven patients had clinically classic disease which was proved serologically by positive heterophil antibody agglutination studies with both guinea pig kidney and beef erythrocyte absorption studies One patient had neither petechial hemorrhages nor a positive heterophil antibody titer but otherwise the case was classic both clinically and hematologically

► [*These are worth noting on physical examination but probably should not be given too much weight as pathognomonic of the disease* Petechial lesions on the soft palate may be seen in rubella streptococcic sore throat and in acute allergic reactions to drugs.—Ed.]

(5) J A M A 161 59 594 J e 16 19 6

Cardiac Involvement in Infectious Mononucleosis Many case reports of cardiac complications of infectious mononucleosis have appeared but the incidence rate is unknown Robert J Hoagland[6] (U S Army Hosp Fort Benning) studied ECG s of 100 consecutive patients hospitalized with mononucleosis

Significant ECG changes were found in only 5% Two patients had minimal P R interval prolongation 1 an increase in Q T duration and a fourth isoelectric T waves in lead II These abnormalities disappeared during the 3d or 4th weeks of illness A fifth patient had complete atrioventricular heart block persisting during 6 weeks of hospitalization and for a follow up of over a year However he had no functional impairment and no subjective physical or roentgenographic indications of heart disease

Discrepancy between these observations and those of other authors who reported more frequent ECG abnormalities is attributed to three differences Unlike others the present report includes all cases of mononucleosis in a consecutive series In this series mononucleosis was not diagnosed unless hematologic and serologic criteria were fulfilled Third only isoelectric low amplitude T waves were regarded as significant and only if there were in leads other than III and $V_{1\ 3}$

Acute pericarditis is a rare complication and has not been encountered in almost 300 patients with infectious mononucleosis

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PROTOZOAN AND METAZOAN INFECTIONS

Fatal Amebiasis Report of 148 Fatal Cases from the Armed Forces Institute of Pathology B H Kean Hugh R Gilmore Jr and William W Van Stone[7] reviewed 290 cases and selected the 148 cases in which amebiasis was the primary cause of death The Far East contributed almost nine times as many cases as Europe

Onset of disease in most cases was acute clinical course rapid and progression to death swift Death occurred in al

(6) Am J M Sc 3 252 257 S ptemb 1956
(7) A I t Med. 44 831 843 M y 1956

most 80% of cases within 6 months of the first reported symptoms and in 20% of these within 2 weeks This is in striking contrast to the popular notion based on the majority of nonfatal cases that amebiasis is a chronic quiescent infection

Of 133 cases in which a clinical diagnosis was recorded amebiasis was correctly diagnosed in 48 (33%) The predominant causes of death were intestinal complications (80 cases) liver disease (31) fatal lung involvement (17) and surgical aftermath (10) Perforation of the intestine with peritonitis was the commonest cause (45 cases), and peritonitis from all causes was fatal in 75 Jaundice was noted in 14% of cases with and without liver abscesses Intestinal perforation was more common in cases without liver abscess Endameba histolytica was demonstrated histologically at autopsy in one third of cases and was not found in one third no specific statement was made in the other third

Amebic abscesses in the liver were found in 90 cases (61%) a proportion considerably higher than previously reported Of 41 liver abscesses that ruptured 22 extended into the lung 10 into the abdominal cavity 5 under the diaphragm 2 into the pericardium and 1 each into the kidney and pancreas

Fever of Undetermined Origin Presumptive Cause Amebic Colitis A case is reported by Murray Strober[8] (U S Air Force Hosp Salina Kan)

Man 29 had been well until 3 months before admission when in Korea he noted anorexia backache slight cough lack of energy occasional tightness in the chest and a rare bout of diarrhea During this 3 months he lost 35 lb He had eaten only government approved food and had no unpasteurized milk but had consumed powdered eggs and milk. He had taken all prescribed malaria medications For 1 month before admission he had chills and fever twice daily Three injections of penicillin 10 days before admission had no effect

Temperature was 102 F hemoglobin 11 8 Gm/100 ml and white blood cell count 10 150 For the first 3 weeks of hospitalization temperatures ranged from 99 to 103 F and he continued to lose weight. Blood cultures were negative All fecal specimens were taken directly to the laboratory but 20 examinations for ova and parasites were negative Proctoscopy was normal to 10 cm and smears of the mucosa were negative for ova and parasites A roentgenogram after a barium enema showed the serrated cecal mucosa with a thickened irregular border (Fig 10)

(8) U S Armed Forces M J 7 1055 1058 July 1956.

Because of the x ray findings the febrile course and recent return from Korea therapeutic trial of an amebicide chiniofon 075 Gm 3 times daily was begun Within 48 hours temperature dropped to 98 F signs of toxicity rapidly disappeared the patient



Fig 10 (Courtesy of Strober M U S Armed Forces M J 7 105 1058 July 1956)

felt entirely well appetite returned and he rapidly gained 10 lb

Although neither trophozoites nor cysts could be found the dramatic response to chiniofon strongly supports the presumptive diagnosis of amebiasis

Acute Myocardial Toxoplasmosis A case is reported by

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(8) U S Armed Forces M J 7 1055 1058 July 1956



Fg 11 (t p) —B l t d l l t Num ou g m t d d l ted lymph t m k d lymphocyt d monocyt filt t on without l t Hem t yl -e d d f m 80
Fg 1 (bottom) —B la t d n d l t d lymph t l f bm Ph s- ph t g t d h mat l d d f m 800
(C tesy f A V M d K pp h E Am J P th 3 1089 1115 Nov Dec 1956)

R E Potts and A Alun Williams[9] Three previous cases have been reported in adults in which diagnosis was based on positive dye and complement fixation tests and which were considered cases of chronic acquired myocardial toxoplasmosis

Man 30 with bronchial symptoms had a temperature of 101 F pulse rate of 128 blood pressure 85/60 and signs of acute pulmonary edema An x ray revealed severe pulmonary congestion with moderate cardiac enlargement An ECG showed left bundle branch block He was considered to have myocarditis of unknown origin

The dye test for toxoplasmosis was positive 1 32 and the complement fixation was positive 1 8 These results were considered significant and pyrimethamine 50 mg daily and sulfamethazine 1 Gm every 6 hours were started There was no clinical response One week before death 60 days after admission transient erythema appeared on the trunk with a few petechial hemorrhages on the left lower chest and the patient had intermittent diarrhea

The main autopsy finding was congestive heart failure There were several small recent infarcts in the right lung The heart was hypertrophied mainly on the right Histologic examination confirmed the microscopic findings There were scattered foci of lymphocytes plasma cells and mononuclear cells but no toxoplasma was found in an extensive search Toxoplasma was isolated from a portion of heart muscle inoculated into experimental animals

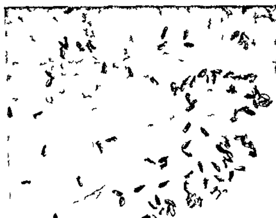
Before the patient became ill his dog had diarrhea and vomiting for 6 weeks This may have been the source of infection

Balantidiasis Review and Report of Cases are presented by Victor M Arean and Enrique Koppisch[1] (San Juan Puerto Rico) Balantidium coli has been found as far north as Finland Sweden and Norway but occurs most frequently in subtropical and tropical zones It has been identified in Canada the United States Mexico Honduras Costa Rica Panama Jamaica Cuba Puerto Rico Venezuela Colombia Brazil Uruguay Argentina and Chile

The parasites are readily identified for they are the largest protozoa infecting man (Figs 11 and 12) Many wild animals are carriers but of the animals in relatively close contact with man the hog is most frequently and heavily parasitized In more than 50% of cases there is a history of contact with pigs

(9) La t 1 483 484 Ap 21 1956
(1) Am. J Path 3 1089 1115 Nov Dec. 1956

in infected water The peripheral venous system is then invaded and the cercariae eventually enter the visceral or portal circulation They mature in the intrahepatic branches of the portal vein and travel back against the blood flow to the mesenteric veins and hemorrhoidal plexus where copulation and egg laying occur The passive transport of eggs within the lumens of the veins to the liver results in local destruction with granulomatous cellular and fibrous reaction These granulomatous areas may progress to cirrhosis and cause



F g 13—Rect l b p y m u m mb t p y (t d) how g l t l p S ma gg f om m 31 P rt R a dm tt d w th l ba pneum la g d l d b m l l f n t n t ts H w a h vy d nk Tw tool xam t on w g t f r p s t and S gm dos opy h wed p ct t e io f m ou m mbr f t d s gm d (Co rt y f W rne B W Am J S g 9 743 747 N mb 1956)

portal hypertension esophageal varices splenomegaly and ascites

In addition to their transport to the liver many eggs are trapped in the smaller venules of the bowel wall Eggs which escape from the venules to the submucosa cause a cellular fibrous granulomatous response with pseudotubercle formation and proliferative polypoid reaction Nonencapsulated eggs pass into the lumen of the bowel and are passed in feces to continue the cycle

In patients with this disease Benjamin W Warner (New York) has noted punctate hemorrhages and erosions dis

( ) Am J S g 92 743 747 N mbe 1956

Balantidiasis usually involves the colon from cecum to rectum but more commonly and severely the rectosigmoid segment Early lesions appear as small flask shaped ulcers a few millimeters in diameter These expand into ulcers re sembling amebic colitis The mucosa about the ulcers may be reddened and swollen or may appear normal Absence of polymorphonuclear leukocytes and an abundance of round cells and eosinophils distinguish balantidiasis from bacterial infections

Whether entering through the surface epithelium or glands the parasite usually *penetrates the basement mem brane* and then the muscularis mucosae to reach the sub mucosa and may be found in dilated lymphatics *The lymph* vessels and blood capillaries become much dilated mucosa and submucosa become necrotic and the limiting portions become infiltrated chiefly with lymphocytes

Clinically the chronic form of the disease is characterized by loose bowel movements alternating with constipation The acute form appears suddenly with 3 15 bowel move ments daily accompanied by tenesmus The stools contain mucus blood and neutrophils In the fulminating type seen ordinarily in emaciated patients or late in some other severe *disease diarrhea starts suddenly with 5 25 bowel move* ments a day Diagnosis depends on identification of the para site in the stools or scrapings obtained at proctoscopy

Prognosis for balantidiasis especially the acute and ful minating types was poor until 1950 Mortality was as high as 30% Antibiotics have improved the outlook Aureomycin® and Terramycin® have been reported useful The dose is 2 Gm daily to a total of 28 Gm

Diagnosis of Schistosomiasis Mansoni by Sigmoidoscopy and Transparency Biopsy of Rectal Mucous Membrane The large influx from Puerto Rico to the United States makes some knowledge of schistosomiasis imperative

In man the disease is directly related to the peculiar life cycle of the worm The cycle is maintained by passage of eggs with a lateral spine from the human host thereby con taminating water containing appropriate species of snails The eggs hatch and release free swimming ciliated larvae which enter the visceral mass of the snail and multiply In about 4 weeks the larvae emerge as cercariae and can pene trate skin or buccal mucous membrane of an

specific antigen or skin test is available for diagnosis The minute size of the lesions and spontaneous healing by fibrosis account for the usual favorable prognosis

John H Dent Robert L Nichols Paul C Beaver G M Carrera and R J Staggers[3] (New Orleans) report a case in a child studied at autopsy who died of overwhelming homologous serum hepatitis and had widespread lesions caused by Toxocara canis larvae

Boy aged 19 months was first seen in November 1952 because of fever abdominal distention and general malaise He had been hospitalized elsewhere for 6 weeks acutely ill with fever a hacking nonproductive cough and abdominal distention Shortly after the acute onset the liver became enlarged Six days of intensive antibiotic therapy including penicillin streptomycin Terramycin® and Aureomycin® was without benefit The hemoglobin level on the present admission was 9 3 Gm /100 ml white blood count 32 000 and eosinophils 59% X rays showed diffuse pneumonitis in the lower half of the right lung field Daily fecal examinations revealed no ova cysts or parasites

Exploratory laparotomy in January 1953 showed numerous small nodules on the liver and biopsy revealed the larvae of T canis The patient received 200 cc. whole blood He improved was discharged and 6 weeks later appeared greatly improved on cortisone daily Eight weeks after surgery he became acutely and severely ill with chills fever and jaundice rapidly became comatose and died Clinical diagnosis was death due to overwhelming homologous serum hepatitis

At autopsy the larvae were seen widely disseminated with an accompanying granulomatous process None of the lesions was visible grossly except in the liver Lesions were found in cardiac muscle liver capsule small bowel muscularis beneath the serosal surface of large bowel renal cortex pancreas mesenteric lymph nodes spinal cord pons cerebellar peduncle and cerebral cortex The minute size and wide distribution in the lungs prevented their detection by x ray

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RHEUMATOID ARTHRITIS

Long Term Results in Early Cases of Rheumatoid Arthritis Treated with either Cortisone or Aspirin Are Examined in a Third Report by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone ACTH and Other Therapeutic Measures in Chronic Rheumatic Diseases[4] A comparative study of the

(3) Am J P th 3 777 803 J l A g 1956
(4) B t M J 1 847 850 Ap 13 1957

crete or in clusters pinpoint or pinhead size without surrounding inflammation on sigmoidoscopic examination Miliary raised granulomas or excrescences of fresh granulation tissue of varying size and varying stages of polypoid formation, from rough irregular outgrowths of tissue to organized polyps may also be present Surprisingly these mucosal changes have not been noted as consistently by others

The technic of rectal mucous membrane biopsy is simple A superficial punch biopsy bite is taken from the edge of the middle rectal valve The tissue is placed on a glass slide teased apart thinned and flattened out A drop of saline is added a cover slip or another slide is placed over the tissue for compression and the specimen is examined under low power as a transparency, without stain (Fig 13) This biopsy technic has yielded positive results in about 65% of clinically suspected cases

Visceral Larva Migrans With Case Report This clinical syndrome is due to invasion of human viscera by larvae of nematodes which are normally parasitic in lower animals It occurs primarily in children and is typified by pronounced and prolonged eosinophilia with or without constitutional symptoms It has been reported as Loffler s syndrome tropical eosinophilia familial eosinophilia benign eosinophilic leukemia or disseminated visceral ascariasis with eosinophilia

In structure toxocara larvae resemble those of the more familiar Ascaris lumbricoides and in their normal hosts—dog and cat—the larvae follow a life cycle similar to that of A lumbricoides in man Children acquire infection by swallowing dirt contaminated with infective ova These hatch in the stomach and intestine and the larvae migrate through the intestinal wall to other organs via blood vessels lymphatics and tissue spaces Infection by A lumbricoides can be diagnosed by examination of the feces for ova or the adult worm but toxocara larvae only uncommonly complete their life cycle in man and rarely if ever reach the egg laying stage in the human intestine Therefore fecal examinations are not contributory to diagnosis of visceral larva migrans

Constitutional symptoms visceral granulomas and eosinophilia make a definite clinical syndrome Species identification is not necessary for presumptive clinical diagnosis No

Carefully planned splenectomy is the only treatment per manently beneficial ACTH occasionally produces a tran sient rise in platelets and leukocytes and a short course 25 60 mg daily for 6 days combined with transfusions is the most effective preparation for splenectomy

Splenectomy has no effect on the joints but the rise in neutrophils platelets and hemoglobin is almost immediate These levels are maintained and may exceed the normal level previously recorded

Amyloidosis in Rheumatoid Arthritis G A K Missen and Jean Duncan Taylor[6] (Postgrad Med School London) surveyed all autopsies over a 19 year period a total of 6 605 In 48 cases a diagnosis of rheumatoid arthritis had been made clinically but was doubtful in 1 Amyloidosis was present in 8 of the 47 and in 6 of these there was no cause for amyloidosis other than the arthritis Sections of joint tissue in each were histologically consistent with rheumatoid arthritis

The two groups of patients with rheumatoid arthritis with and without amyloidosis were similar in mean age at death and in activity of the arthritis Of those with amyloidosis 6 had proteinuria and uremia was the principal cause of death in 4 Distribution of amyloid in liver kidneys spleen and adrenals was characteristic of secondary amyloidosis seen in suppuration of long duration The only organ whose func tion is significantly impaired by amyloid deposition is the kidney When secondary amyloidosis directly causes death it is usually through renal failure

Among the 6 605 autopsies surveyed secondary amyloid osis was recorded in 43 cases including the 8 of rheumatoid arthritis in 15 of these death was due to uremia but in only 3 was there kidney disease other than amyloidosis

Analysis of all postmortem series in the literature gave a conservative incidence of 14 9% amyloidosis in rheumatoid arthritis In the series reported here incidence was 13 3% This may not represent the incidence of amyloidosis among all rheumatoid patients since selective factors in various hospital populations differ However secondary amyloidosis complicates rheumatoid arthritis in a significant number of cases

(6) J P th & B t 71 179 192 J ry 1956

value of cortisone and aspirin therapy in early cases of rheumatoid arthritis was started in 1951 The therapeutic trial was not continued after the second year but most of the 61 patients in the original series have been followed by the physicians at 5 participating centers A review of the condition of these patients 3-4 years later revealed some interesting facts

The progress of the patients with early rheumatoid arthritis was probably not better than that of patients in other series with various treatments and with a disease lasting less than 1 year In a fourth of the patients the disease went into remission in a fourth it remained active and in the rest it remained slightly active Whether the patients were originally given aspirin or cortisone therapy did not influence the outcome In time 7 patients were transferred from cortisone to aspirin whereas none were transferred from aspirin to cortisone Serious complications though few were seen only in patients receiving cortisone No significant differences were noted in the two groups at follow up but the changes in therapy suggest that as time passes both patients and physicians sometimes come to prefer aspirin to cortisone therapy

In the long term management of rheumatoid arthritis at least during the first 4 years aspirin therapy is apt to prove more satisfactory than cortisone though some patients derive more relief from cortisone

► [The findings in this long term co-operative clinical test are worth careful study It is interesting to reflect that although rheumatoid arthritis was the disease in which the dramatic anti inflammatoy effects of cortisone were first observed little or no convincing evidence of long term benefit has been forthcoming —Ed.]

Felty s Syndrome reviewed by L Cudkowicz[5] (London) was first described in 5 adults who had gradually progressive arthritis neutropenia splenomegaly and skin pigmentation and in 3 lymphadenopathy The hypersplenism causes pancytopenia The total white cell count may be as low as 750 and the platelet count less than 100 000 The hemoglobin value is diminished Liver function is not grossly impaired, and biopsies have shown normal structure These observations may occasionally differentiate portal hypertension and amyloid disease which may occur in long standing rheumatoid arthritis from Felty s syndrome

(5) Rh matism 12 37-41 April, 1956

usually full though painful Rheumatic nodules and rashes may appear in the skin Vomiting and diarrhea although not invariable show the generalized nature of the disease also reflected in the pyrexia tachycardia anemia and loss of weight

Examination reveals only muscle pain limited limb movement occasional enlarged lymph nodes and rarely an enlarged spleen Most cases present as pyrexia of unknown origin especially if aching succeeds the fever An extremely high erythrocyte sedimentation rate is characteristic Hemoglobin is decreased and the white blood cell count is usually normal

Observations are reported on 21 patients with the rheumatoid syndrome The differential sheep cell agglutination test done on 14 was strongly positive in 5 Of the 21 15 had hypochromic anemia resistant to iron therapy at some time during their illness The lowest sedimentation rate in the series was 25 mm in 1 hour the highest 148 mm in 1 hour (Westergren) Four patients had identical symptoms but in addition had minimal transitory involvement of joints These probably represented a link from true rheumatoid arthritis

Response to therapy with salicylates is fair Prognosis is invariably good but the illness may persist for months or years with remissions It is suggested that this syndrome be called anarthritic rheumatoid disease

► [This sounds like a rather specific entity and the author reports having seen 21 instances of it I wonder what the rest of us have been calling it? —Ed.]

COLLAGEN DISEASES

Six Years Survival in Severe Systemic Lupus Erythematosus Study of 12 Cases is presented by John R Haserick[9] (Cleveland Clinic) During this period they saw a larger group with this disease who survived but since they were at no time as ill their survival is unremarkable The 12 patients presented were not expected to live Systemic lupus erythematosus is so complex clinically and therapeutically that it is impossible to evaluate any treatment program statistically Results of this study were judged clinically

(9) Con ect t M J 20 617 626 A gu t 1956.

Rheumatoid Arthritis with Chronic Leg Ulceration. Six patients were presented by J H Allison and F Ray Bettley[7] (Middlesex Hosp London) All had severe crippling and apparently typical rheumatoid arthritis with many subcutaneous nodules Appearance of the ulcers was so characteristic that the cases could be recognized by examining the ulcer alone

In most cases the ulcers were on the lower third of the leg on the inner or outer surface in one just below the knee and in another the toe and foot Onset was not observed The earliest sign was a painful induration about 1 cm across which in 1 2 weeks broke down to form a punched out ulcer The largest were 10 cm across always with smooth even outlines Granulations did not form readily Surrounding erythema and induration were not prominent Subcutaneous edema was slight or absent None had varicose veins antecedent phlebitis or other evidence of vascular stasis Leg pulses and skin temperature were normal In 4 of the 6 L E cells were found in peripheral blood 4 had drug eruptions in the past and many other symptoms of great variety were compatible with diagnosis of disseminated lupus erythematosus Histologic studies suggested the primary lesion was collagen necrosis It may be the same as that which causes a rheumatic nodule in deeper tissue forming an ulcer or a proliferative tissue reaction Failure of grafting in 3 patients was particularly striking

Anarthritic Rheumatoid Disease This syndrome affects elderly persons and is remarkably similar to the prodromal symptoms of rheumatoid arthritis It has previously been described and is further delineated by L Bagratuni[8] (Radcliffe Infirm Oxford England) It occurs in middle aged and elderly men and women and starts as a pyrexial illness with sweating loss of appetite and weight anemia and general malaise There is often abdominal discomfort flatulence vomiting or diarrhea headache generalized aching most severe in the neck shoulders and back stiffness of muscles and paresthesias in the limbs The pain in the neck shoulders and back is so severe that active movement is often impossible although there is no obvious arthritis Passive movement is

(7) Lancet 1 288 290 Feb 9 1957
(8) Ibid. 2 694-697 Oct. 6 1956

hypertensive patients treated with large doses of hydralazine hydrochloride (Apresoline®) develop a syndrome simulating collagen disease manifested by several of the following symptoms arthritis fever weakness weight loss hepatomegaly splenomegaly anemia leukopenia reversed serum albumin globulin ratio and in a few L E cells in the peripheral blood

Phillip Comens (Washington Univ) fed dogs hydralazine in horse meat After about 30 days the animals began to exhibit decreased appetite and weight loss Doses approximated the maximum used in treatment of human arterial hypertension

The animals manifested weakness weight loss anemia altered electrophoretic patterns of serum proteins leukopenia hyperglobulinemia and hypocholesteremia Of the 8 animals 7 had L E cells in the peripheral blood and the other had hematoxylin bodies Pathologic specimens of the kidneys revealed changes consistent with those found in disseminated lupus erythematosus

► [In a similar study Gardner (Brit J Exper Path 38 227 1957) came to somewhat different conclusions he did not regard the illness in dogs given hydralazine as having much resemblance to disseminated lupus erythematosus or think that a true LE phenomenon could be demonstrated —Ed]

Treatment of Polyarteritis Nodosa with Cortisone Results after One Year are considered in a report to the Medical Research Council by the Collagen Diseases and Hypersensitivity Panel[3] To learn whether it improves the expectation of life and well being in patients with polyarteritis nodosa cortisone was given to those fulfilling the criteria for diagnosis and their fates were compared with those of patients selected retrospectively by the same criteria The analysis is based on 17 patients

The retrospective control group was obtained by searching the diagnostic indexes clinical and pathologic of the hospitals providing most of the treated cases and by collecting all cases proved by biopsy from 1946 to 1950 when cortisone was introduced

In patients with severe constitutional illness the initial effects of cortisone were always definite and often dramatic Within 2 3 days fever abated appetite and well being improved and joint and muscle pains decreased Early weight

( ) J Lab & Cl M d 47 444 454 M h 1956
(3) B t M J 1 608 611 M 16 1957

One patient received neither cortisone nor corticotropin Eleven received steroid therapy in one or more forms Two did not require cortisone or corticotropin for 2 years then they relapsed and hormone therapy was resumed Clinical remissions were stable enough to allow dental extractions major abdominal and chest surgery fracture setting pregnancy and repeated sun exposures In most instances special precautions were taken and patients were usually provided with booster doses of steroids and antibiotics Even if steroids had been discontinued for some time they were resumed *temporarily during the anticipated stress* *Urinary* changes in the group were of special interest Proteinuria increased casts and erythrocytes occasionally cleared completely during remission

► [It is impressive to read some of the histories in this series and to have this long follow up showing that amelioration took place in so many cases observed in one clinic —Ed]

Pregnancy and Lupus Erythematosus According to Emanuel A Friedman and James W Rutherford[1] (Columbia Univ) lupus erythematosus does not specifically alter fertility but the incidence of abortions and premature births is increased Infants carried to viability seem unaffected by the maternal disease

Most patients with acute or subacute disseminated lupus erythematosus have notable subjective relief and occasionally reversal of laboratory abnormalities during pregnancy The basic disease process is not specifically affected by pregnancy *Exacerbations and remissions in early pregnancy* are about equally frequent There is usually no change during the 3d trimester The disease resumes its prepregnancy status post partum usually within 2 months Exacerbations are the rule since so many become clinically quiescent during pregnancy Rarely the disease process is accelerated rapidly but this may be due to chance unrelated to the pregnancy

No real beneficial effect on the course of the disease can be expected from therapeutic abortion In fact the exacerbation likely to occur postoperatively in a patient already seriously ill may be overwhelming

Experimental Hydralazine Disease and Its Similarity to Disseminated Lupus Erythematosus Between 8 and 15% of

(1) O & Gynec 8 601 610 Nov mbe 1956

hypertensive patients treated with large doses of hydralazine hydrochloride (Apresoline®) develop a syndrome simulating collagen disease manifested by several of the following symptoms arthritis fever weakness weight loss hepatomegaly splenomegaly anemia leukopenia reversed serum albumin globulin ratio and in a few L E cells in the peripheral blood

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(2) J Lab & Cl Med 47 444 454 M h 1956
(3) B t M J 1 608 611 M 16 1957

gain was usually noted The commonest side effect was edema noted in 6 patients Glycosuria was also seen and 1 patient had a perforated gastric ulcer

Retrospective controls are of little value even though the differences are minimized by taking treated and control patients from the same institutions and choosing consecutive periods The two series were closely comparable except that the incidence of hypertension was much higher in the control than in the treated group This is important since hypertension greatly influences prognosis If the hypertensive cases are included the results seem better in the treated series but if omitted the differences are small though still in favor of treatment Since the numbers are so small and the series dissimilar in an important respect comparing them does not justify conclusions about the effect of cortisone on life expectancy in polyarteritis nodosa However results indicate that cortisone may prolong life

Cortisone in polyarteritis nodosa nearly always improves symptoms conspicuously and suppresses the major manifestations of active disease To maintain suppression may require doses of cortisone which provoke troublesome and occasionally dangerous side effects Whether the treatment is better or worse than the disease is as yet undecided

► [An interesting by product of this study is that it illustrates how uncommon periarteritis nodosa is—only 17 cases being collected in 11 large general hospitals over a period of something more than a year One might expect that 5 or 10 times as many cases of disseminated lupus erythematosus would have been observed in the same period —Ed.]

DISEASES OF UNKNOWN ETIOLOGY

Myalgia Cruris Epidemica Ake Lundberg[4] (Karolinska Inst Stockholm) observed an illness in 1955 which mainly affected children often in the same school class or family Onset was acute with high fever and prodromal symptoms of headache and slight catarrhal manifestations Fever lasted about 4 days the prodromal symptoms slightly less When these subsided and fever was in the final stage severe pain appeared in the calf muscles often preventing walking Maximal pain coincided with first normal temperature The pain lasted about 3 days after which patients were completely

(4) Acta paed at 46 18 31 January 1957

asymptomatic The illness lasted approximately a week

Most affected persons were under age 12 only 4 were over 15 Seasonal distribution showed accumulation from the middle of March to the end of April Nausea and vomiting appeared in 41% but few had diarrhea Although the calf muscle pain was excruciating inspection of the calf showed nothing abnormal and no swelling On palpation there was tenderness in a circumscribed area of the fleshiest part of the calf Biopsy in 2 cases showed unspecific degenerative changes Lumbar puncture in 17 showed no abnormalities White blood cell counts in 25 were mostly below 6 000 during the acute phase with subsequent return to normal Therapy was symptomatic In all cases observed prognosis was excellent

Granulomatous Orchitis With Report of Case is described by J A Myburgh (Johannesburg)

Man 58 for 2 months had an aching and heavy feeling in the left testis which became enlarged He had no other symptoms The right testis was normal to palpation The left was about twice as large smooth and hard Sensation was absent The epididymis was slightly enlarged hard and nodular but freely movable The vas deferens was normal Tests for syphilis were negative urine cul



F g 14—Body f t t d low p w h w g t b les c mplet ly epl d by g l m t g f p th l d ll S l g t ll bl Th wa case t ou nd n d f st ba ll Ther w t t l infiltrat on f lymphocyt d pla ma ll (Co rt y f Myburgh J A South Africa M J 30 1230 1233 Dec mbe 2 1956)

(5) South Af M J 30 1230 1231 Dec mbe 2 1956

tures were negative for tuberculosis and a Mantoux test was positive with 1/100 old tuberculin

The lesion was thought to be seminoma The smooth hard enlargement of the body of the testis with absence of testicular sensation was unlike tuberculosis The lesion proved to involve the body of the testis (Fig 14) and the epididymis with the appearance of granulomatous orchitis

Diagnosis rested between sarcoidosis affecting mainly if not solely the testis and granulomatous orchitis Involvement of the testis in generalized sarcoidosis has been described but none comparable to this case The histology in this resembled closely that described in 12 cases previously reported and designated granulomatous orchitis

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FEVER

Role of Leukocytes in Initial Action of Bacterial Pyrogens in Man *After bacterial pyrogen is intravenously injected in* man fever does not begin for at least 45 minutes In the rabbit and man this latent period is shortened if the pyrogen is first incubated with fresh blood This finding suggests that the initial phase of the response is a reaction between the pyrogen and a constituent of blood which results in the release of a new substance

W I Cranston F Goodale Jr E S Snell and F Wendt[6] (London) *confirmed this differentiation of a rapid* and a slow response the type depending on whether the pyrogen was first incubated with fresh whole blood However incubation with human plasma or serum did not accelerate the fever response After injection of pyrogen which had been incubated in blood rich in white cells fever was again rapid in onset When incubated in blood poor in white cells onset of the fever was slow About 150 000 000-200 000 000 leukocytes are needed to produce detectable amounts of rapidly acting pyrogen Granulocytes may be the most important cells in this respect

► [An interesting and important piece of clinical investigation There is other evidence suggesting that a product of the polymorphonuclear leukocyte can affect thermoregulation —Ed.]

Reaction of Patients with Typhoid Fever to Administration of Aspirin has been recognized for many years by physicians in Cape Town Four typical cases are reported by

(6) Cl Sc 15 19 6 M y 1956

Eugene Dowdle[7] (Cape Town) The reaction is characterized by a sudden temperature fall to subnormal level collapse sweating and bradycardia in excess of the usual antipyretic and diaphoretic action of the drug Not all patients react in this way and it may not occur in the same patient if given another dose of aspirin

CASE 1—Man 20 had headache malaise and fever for 4 days The day before hospitalization he had been given 2 tablets of aspirin phenacetin and codeine Profuse sweating weakness and collapse followed On admission temperature was 103 F and the abdomen was distended. Chloramphenicol was administered after the blood was cultured His condition remained unchanged for 3 days and on complaining of a severe headache he was given 2 more A P C tablets whereupon the temperature fell 7 4 degrees in 2 hours. He was gravely ill pale in a state of collapse and prostration with sweating and bradycardia He did not return to his former clinical state for 7 hours

CASE 2—Man 22 admitted with headache malaise and abdominal discomfort received two 5 gr tablets of aspirin He lapsed rapidly into a state of asthenia and prostration with sweating and bradycardia and the temperature fell 6 4 degrees from 10_ F in 2 hours The symptoms subsided and temperature returned to 102 F after 5½ hours

CASE 3—Woman 21 admitted with headache fever and abdominal pain received 2 A P C tablets with no apparent ill effect Two days later he received 15 gr aspirin followed by a sharp temperature drop to 95 F with sweating collapse and bradycardia lasting for 5½ hours

CASE 4—Man 29 with headache toxemia fever and general malaise on admission had a high temperature and moderate splenomegaly Two tablets of aspirin phenacetin and codeine were administered and the temperature dropped to 96 F The patient remained in collapse for 6 hours

► [There seldom is need for antipyretic drugs in the treatment of infectious diseases Symptomatic relief can usually be given with codeine ice bags etc The course of the body temperature is a valuable indication of the effect of antimicrobial agents In any event if aspirin is thought to be indicated it should be administered regularly every 3 or 4 hours to maintain the antipyretic action Otherwise the result is a series of sweats and chills causing additional suffering to the patient —Ed]

BACTEREMIA

Studies on Bacteremia I Mechanisms Relating to Persistence of Bacteremia in Rabbits Following Intravenous Injection of Staphylococci Pathogenic coagulase positive

(7) South Af ca M J 30 474 4 May 19 1956

staphylococci are avidly phagocytized by human leukocytes *in vitro* whereas *pneumococci streptococci and Klebsiella* are rarely ingested David E Rogers[8] (Cornell Univ) introduced large numbers of *staphylococci* into the blood stream of rabbits by a single injection

Indwelling polyethylene venous catheters were used to obtain rapid repeated blood samples during observation By differential centrifugation of the blood sample and culture of the supernatant the number of viable micro organisms contained within leukocytes could be estimated

Staphylococci were cleared from the blood stream during the initial 10 15 minutes after intravenous injection A subsequent abrupt decline in the rate of clearance ensued resulting in a low grade bacteremia demonstrable for hours This strain of staphylococci was rapidly phagocytized in the vascular system of rabbits and viable staphylococci circulated within the cytoplasm of polymorphonuclear leukocytes

The removal mechanisms contained in the liver and spleen *appear preferentially to trap circulating extracellular staphylococci* When most of the circulating staphylococci are contained in leukocytes splanchnic removal declines or virtually ceases The observations suggest that viable intracellular micro organisms are responsible for the persistence of staphylococcic bacteremia in rabbits after the phase of rapid removal

► [A first rate piece of experimental work The demonstration that viable cocci are protected from trapping by the reticuloendothelial system while circulating within polymorphonuclear leukocytes provides an explanation *for the persistence of low grade bacteremia long after intravenous injection* of the organisms —Ed.]

Shock of Bacterial Infection Report of Three Cases Due to Pneumococcic Pneumonia is presented by Robert P Gilbert[9] For pneumococcic pneumonia treatment must be prompt and energetic to prevent death The existence of this form may be overlooked now that most pneumonias can be readily managed by antibiotics Several features should warn the physician that the situation is critical Hypotension is striking and is the first and most definite sign Two of the 3 gravely ill patients were *alcoholics and it is well known* that alcoholics withstand infection poorly and are more sus

(8) J Exper Med 103 713 742 June 1 1956
(9) Quart B ll N rthwe t rn U v M S hool 30 112 116 S mm 1956

ceptible to shock Leukopenia was found in the 2 fatal cases and is a well recognized sign of overwhelming infection The degree of fever is unreliable as an indication of the seriousness of pneumonia

CASE 1—Man 43 an alcoholic had chest pain cough and brown sputum for 10 days On admission he had leukopenia hypotension and bacteremia Treatment was delayed several hours and he died in shock despite large doses of penicillin

CASE 2—Man 54 a moderate drinker had dyspnea weakness and mild chest pain for 3 days He had hypotension minimal fever leukopenia and auricular fibrillation alternating with flutter which diverted attention from the pneumonia Blood cultures later revealed bacteremia Antibiotic treatment was delayed He died in shock 48 hours after admission

CASE 3—Man 51 a fairly heavy drinker was admitted with pneumonia hypotension marked leukocytosis auricular fibrillation bacteremia and moderat fever The hypotension rapidly improved with antibiot cs fluids and oxygen therapy

► [So much is being said about the role of endotoxin in bacteremic shock (see following abstract) that it seems worth while to point out that shock also occurs with pneumococcic bacteremia as in these 3 cases yet the pneumococcus doesn t contain endotoxin —Ed]

Bacteremic Shock The sphygmomanometer is important in recognition and management of certain infections Often vascular collapse associated with bacteremia may not be detected because the usual manifestations of shock are absent or obscured by warm skin bounding pulse and fever William J Martin and Donald R Nichols[1] recently reviewed 137 cases of bacteremia due to gram negative bacilli and found hypotension as a manifestation in 7

The genesis of bacteremic shock is unknown Blood volume does not decrease significantly A bacterial endotoxin has been suggested which affects the vascular system and produces vasodilatation or perhaps causes central vasomotor paralysis with resultant vascular collapse

In patients with gram negative bacteremia the genitourinary tract was the portal of entry in about 60% Any patient with disease of or recent operation on the urinary or gastrointestinal tract who has fever should be suspected of having gram negative bacteremia Blood cultures should be obtained and blood pressure watched closely By detecting hypotension in such patients it is occasionally possible to predict positive blood cultures In patients wi h known bacteremia frequent blood pressure recordings should be

(1) P oc Staff Meet M y Cl n 31 333 340 M y 30 1956

made until bacteremia is controlled Hypotension most frequently recognized as an initial manifestation may supervene during the infection

In patients with chronic urinary tract disease who develop azotemia it is difficult to know whether this is a complication or represents terminal renal insufficiency due to the primary disease The prognosis is graver in such patients Perhaps terminal renal insufficiency is actually precipitated by the further insult of hypotension or perhaps the previously damaged kidneys are unable to recuperate from the hypotension

About 10% of patients with gram negative bacteremia have diabetes mellitus If fever not readily explainable develops in such patients blood should be cultured The complication of bacteremia should be suspected especially if urinary infections are present Shock and bacteremia can be confusing in a patient with diabetes

During hypotension treatment is aimed at restoring circulation before renal ischemia produces organic renal damage Vasopressor agents should be administered quickly During oliguria the aim is to keep the patient alive long enough for the kidneys to recover function Water should be given in amounts sufficient only to replace losses

Antibiotics of the tetracycline group combined with streptomycin are usually efficacious in bacteremia due to gram negative bacilli except those due to pseudomonas In these use of polymyxin B (Aerosporin®) is justified Continuous intravenous administration of levarterenol is effective in managing the shock Steroid hormones do not lessen shock and when administered experimentally to animals given an intravenous injection of meningococcus toxin they neither prevent nor accentuate the shock Whole blood plasma or dextran has no demonstrable effect

► [Whenever shock is encountered the possibility of overwhelming infection must be thought of The clinical picture of shock and pneumonia for example has been interpreted as due to acute myocardial infarction —Ed]

Acute Meningococcemia with Vascular Collapse Analysis of 10 Recently Treated Cases is presented by Donald M Kanter *Dominic A Mauriello and Norman Learner*[2] Before sulfonamides were available this combination was al

(2) Am J M Sc 232 674-687 December 1956

most universally fatal Classic features are petechial eruptions shock and adrenal hemorrhages seen at autopsy Sulfonamides and penicillin greatly improved the prognosis in all types of meningococcic infection but mortality in the Waterhouse Friderichsen syndrome remains high

The 10 cases reported were seen at an Army hospital between 1953 and 1955 and comprised 11% of all admissions there for meningococcic disease The mortality was 50% despite use of adrenal corticoids norepinephrine sulfonamides and antibiotics Of the 5 patients who survived 2 had residual myocarditis requiring prolonged convalescence and eventual separation from the service None of these had evidence of chronic adrenal insufficiency It is probable therefore that the survivors did not have massive adrenal hemorrhage with extensive destruction of glandular tissue but rather an acute functional adrenal insufficiency

For treatment of acute meningococcemia with vascular collapse the following regimen is recommended An initial dose of 1 000 000 units of aqueous crystalline penicillin intravenously is followed by 1 000 000 units intramuscularly every second hour Sulfadiazine or Gantrisin® intravenously should be used concurrently Gantrisin® should be given initially as 4 Gm in 500 ml of 5% glucose in water intravenously during 1 hour followed by 4 Gm in 1 000 ml of 5% glucose at a rate which will give blood levels of 10 15 mg Gantrisin®/100 ml Between 10 and 18 hours of treatment are necessary to produce such levels Rigid restriction in the amount of intravenous fluid given during the first 24 36 hours is important No saline should be given since myocarditis is such a frequent complication Because hydrocortisone and other corticosteroids cause massive retention of sodium and water they may precipitate acute congestive failure Rapid digitalization with lanatosid C intravenously is advisable as soon as diagnosis is established To keep intravenous fluids safely between 2 500 and 3 500 ml /24 hours norepinephrine should be concentrated At least 24 mg Levophed® bitartrate in 500 ml of 5% glucose in water should be given rather than 1 ampule in 1 000 ml as is commonly used Hydrocortisone should be given initially as 100 mg in 500 ml of 5% glucose in water by slow intravenous drip over 6 hours followed by 50 mg intramuscularly every 6 hours during the critical phase of the illness

HOST FACTORS IN INFECTIONS

Hazard of Severe Infections in Splenectomized Infants and Children is re emphasized by Carl H Smith Marion Erlandson Irving Schulman and Gertrude Stern[3] (Cornell Univ) who extended their initial observations and found heightened susceptibility to severe infection in a group of infants and children in whom the spleen was removed for various reasons mostly hematologic These untoward circumstances in the immediate and remote postoperative period could not be unequivocally attributed to splenectomy but the relation seemed more than fortuitous

There were 19 cases of fulminating severe infections ending in death in 6 Except for 2 cases of traumatic rupture of the spleen the major indication for splenectomy was an established blood disorder Infections fell into several well defined categories meningitis acute benign pericarditis (in patients with Cooley s anemia) acute endocarditis and sepsis Pneumococcus was the most frequent bacterium isolated and meningitis the most frequent clinical diagnosis Pneumococcic meningitis predominated in this and other reported series In most the interval between splenectomy and infection was 2 years or less ranging from 1 day to 16 years Age at splenectomy ranged from 13 months to 17 years None of the patients had diminished gamma globulin

These and other similar cases recently reported suggest more than a random association between splenectomy and susceptibility to infection Experiments have implicated the spleen in fundamental processes of resistance to infection The number reported is small compared to the ever increasing number of splenectomies Nevertheless although benefits of splenectomy are substantial and well documented potential hazards demand that exact criteria be established in selecting patients for the operation The young patient who has had splenectomy requires close supervision for several years postoperatively so that immediate and energetic treatment may be instituted in the event of sudden and severe illness

► [The same susceptibility to infection has been observed occasionally in

(3) Am. J Med. 22 390-404 March 1957

adults following splenectomy although it seems to be much commoner in children —Ed]

Association of Salmonella Enteritis with Operations on the Stomach William R Waddell and Lawrence J Kunz[4] (Massachusetts Gen l Hosp) report that of 34 patients with salmonella infection 9 (26%) had previously undergone gas tric operations In several the enteric infection developed 1 8 years after surgery The apparently high proportion of salmonellosis in patients who had previous gastric surgery suggests that these patients run a considerably higher risk of contracting bacterial gastroenteritis than the average hos pital patient Changes in the physiology of the alimentary tract known to occur after gastric surgery may be sus pected of altering the susceptibility of the patient to enteric infection

Two changes in gastrointestinal function that might pre dispose these patients to infection are relative or absolute achlorhydria and rapid emptying of food into the small in testine immediately after ingestion with rapid transit through the small intestine into the colon Other changes such as altered normal bacterial flora or hydrogen ion concentration in the intestine may be equally significant Regardless of the cau e it is posulated that after major gas tric surgery patients may be susceptible to enteric patho gens that under more normal circumstances would never become established

(4) N w E gl d J Med 255 555 559 S pt 20 1956

The Chest



CARL MUSCHENHEIM MD

PART II

THE CHEST

PATHOLOGY

Histochemical Study of Pulmonary Hyaline Membrane At autopsy on premature infants microscopic examination of the lungs often reveals eosinophilic material which forms a hyaline membrane in the alveoli and bronchioles This membrane is closely associated with intense respiratory distress observed clinically There is no general agreement on its pathogenesis

F Duran Jorda A Holzel and W H Patterson[1] (Manchester England) compared the hyaline membrane of infants with eosinophilic material occasionally found in pulmonary edema or other parts of the body such as in thrombosed vessels or in the albuminous precipitate surrounding some glomeruli The different precipitates behaved similarly (table) Results suggested that the hyaline membrane belonged to the group of cytochromes derived from

STAINING REACTIONS

S	H AL N M M E	P M ARY E MA	TH M	G M U U PREC
Haematoxylin and eosin	Red	Red	Red	Red
Periodic acid Schiff	Pos tive	Positive	Positive	Positive
Southgate s mucicarmine	Brownish	Browni h	Brownish	Brownish
Prussian blue	Negative	Negative	Negative	Negative
Van Gie on	Yellow	Yellow	Yellow	Yellow
Thionine	Negative	Negative	Negative	Negat ve
Methylene blue	Negative	Negative	Negative	Negative
Phloxine tartrazine	Red	Red	Red	Red
Carbol fuchsin	Yellowish	Yellowish	Yellowish	Yellowish
Congo red	Negative	Negative	Negative	Negative
Gram Weigart	Negative	Negative	Negative	Negative
Gentian violet	Faint	Faint	Faint	Faint
Sudan IV	Negative	Negative	Negative	Negative
Mallory s tr chrome	Orange	Orange	Orange	Orange
Masson s trichrome	Redd sh	Reddish	Redd sh	Reddish

(1) Arch D Ch ldh od 31 113 118 Ap l 1956

blood proteins and pigments All the materials examined gave a positive peroxidase reaction

Ultraviolet light showed a definite primary fluorescence in the hyaline membrane The membrane also showed absorption in the same region of the violet band as the blood in capillary vessels These findings were confirmed under a mercury vapor lamp To eliminate the possibility of the membrane consisting of fat or glucoproteins (mucus) sections of



Fig 15—Section of lung with hyaline membrane Hematoxylin-eosin (C t sy f D n J d F s l \ h D Childhood 31 113 118 Ap 1 1956)

the lung with hyaline membrane were submitted to micro incineration A selected microscopic field of the same section was photographed and then incinerated (Fig 15) Examination of the same field with a dark condenser showed that the hyaline membrane left considerable ash some red indicating the presence of iron salts and silica Amniotic fluid was eliminated as the source of hyaline membrane since after dialysis the residue was composed entirely of epithelial cells without eosinophilic material

These investigations indicate that the membrane is derived

from the lung capillaries It evidently follows intense con gestion of the alveolar capillaries which results in an exuda tive process through the capillary walls It seems to be an end result rather than a cause and can be explained without postulating aspiration of amniotic fluid

Primary Pulmonary Vascular Disease Report of 5 Cases is presented by Harry M Carpenter and Robert W Prichard (Winston Salem N C) Pulmonary vascular lesions are clas sified as 5 general types hyperplasia of intimal elastic tissue endothelial proliferation fibrosis of the media endarteritis obliterans and hypertrophy of the media The first 4 are gen erally associated with chronic pulmonary inflammatory dis ease or are secondary to extrapulmonary causes Hypertro phy of the media is described in mitral stenosis systemic hypertension and congenital heart disease with systemic right ventricle

A hypothesis for pathogenesis of primary or congenital hy pertrophy of the media of pulmonary arterioles is that it rep resents persistence of the state of these vessels during intra uterine life when resistance is high in intrapulmonary cir culation and blood is shunted through the ductus arteriosus This is reflected in the thick walled pulmonary vessels found at birth

Primary pulmonary vascular disease (hypertrophy of the media hyperplasia of the intima or both) is a rare but defi nite entity that occurs mainly in children No authentic case has been described beyond the second decade Criteria for diagnosis are adequately demonstrated hypertrophy of the media or hyperplasia of the intima involving pulmonary ar teries less than 100 μ in external diameter absent segmental endarteritis necrosis and infarcts and absence of known causes of secondary sclerosis of pulmonary vessels The au thors 5 patients presented no thromboembolism and the reaction did not seem to be secondary to inflammation All 5 had a relatively prolonged history of respiratory difficulty and clinical symptoms suggested congenital heart disease At autopsy all showed extensive thickening of the media of the pulmonary arterioles with hypertrophy particularly of the right ventricle The disease probably is a congenital anomaly

(2) Am J Cl P th 26 899 909 Aug 1956

Plethysmographic Determination of Volume of Gas Trapped in Lungs The volume of trapped gas is that component of thoracic gas volume which having entered the thorax is present in the lungs or pleural space but unable to leave because of intrapulmonary mechanical factors which prevent gaseous outflow This has not been studied previously in man because a method of measuring the volume was not available By use of a body plethysmograph George N Bedell Robert Marshall Arthur B DuBois and Julius H Comroe Jr[3] (Univ of Pennsylvania) studied 36 patients This method measures the volume of all gas in the thorax whether in communication with the airway or not in contrast with dilution and compression methods which measure only that volume of gas which is in communication with the airway during the test

If mean thoracic gas volume measured by the plethysmograph significantly exceeded the functional residual capacity measured by the dilution method trapped gas was present Thoracic gas volume minus washout volume is the volume of trapped gas In patients with pneumothorax pulmonary cysts emphysema and intrathoracic or pulmonary tumors (conditions in which trapping of gas occurs) the *thoracic gas volume* exceeded the *washout volume* by a significant amount more than 0 44 L In a patient with pulmonary cysts and emphysema the excess volume the trapped gas was 3 67 L In patients with other cardiopulmonary or thoracic disorders no significant amount was found

In patients with emphysema measurements indicated that either the orifices to some alveoli were completely closed to outflow or the alveoli were so poorly ventilated that the dilution method underestimated the volume of contained gas Total lung capacity is erroneously measured by the 7 minute method in patients with emphysema and is reported too low Plethysmographically thoracic gas volume in 11 patients was greater than predicted values for healthy men of the same age Estimation of absolute values and the conclusions drawn from published values of residual volume functional

(3) J Cl I vest 35 664-6 0 Jun 1956

residual capacity and total lung capacity will probably have to be revised in patients with emphysema

Combining the plethysmography volume with the wash out volume provides a method for studying gas trapping and for investigating true residual volume and total lung capacity in patients with certain pulmonary diseases

Viscous Resistance of Lung Tissue in Patients with Pulmonary Disease In normal subjects about a sixth of the nonelastic resistance of the lungs is viscous resistance the rest is airway resistance In asthma and emphysema resistance is *considerably increased* Robert Marshall and Arthur B Dubois[4] (Univ of Pennsylvania) studied patients with pulmonary sarcoidosis pneumoconiosis pulmonary infiltrations asthma emphysema kyphoscoliosis cardiovascular *disease and miscellaneous diseases using a new method in* which tissue resistance is calculated as the difference between total pulmonary resistance measured by the esophageal balloon and airway resistance measured by the plethysmograph

In diseases involving lung parenchyma the tissue viscous resistance is often raised but the increase is seldom a major part of the work of breathing In such diseases lung compliance shows greater variation and causes increased impedance to breathing In asthma and emphysema although tissue resistance may be increased increased airway resistance is the disabling factor

A moderate increase in viscous resistance of lung tissue was found in patients with sarcoidosis pulmonary fibrosis asthma and kyphoscoliosis There was also some increase in tissue resistance in 3 of 7 patients with emphysema but in *none was the increase marked*

Renal Circulation in Chronic Pulmonary Disease and Pulmonary Heart Failure was investigated by C H Stuart Harris J MacKinnon J D S Hammond and W D Smith[5] *(Univ of Sheffield) The cause of congestive heart failure* in chronic pulmonary disease is unknown The commonest precursors are chronic bronchitis and emphysema This type heart failure is not accompanied by the usual peripheral vaso constriction and low cardiac output but *renal circulation is*

(4) Cl S 13 473-483 No embe 1956
(5) Quart. J M d. 25 389-405 J ly 1956

restricted to about the same level as that found in valvular heart disease

Renal circulation ascertained by clearance technics was the same in 18 *patients recently recovered from congestive* heart failure due to chronic pulmonary disease as in 22 with chronic pulmonary disease who had never had heart failure During the congestive phase of cor pulmonale in 26 patients both glomerular filtration rate and renal plasma flow were significantly under the levels found in recovery from failure in 18 patients Renal blood flow was similarly depressed and filtration fraction raised during heart failure these were reversed during recovery

In 10 patients with chronic pulmonary disease (chronic bronchitis and/or bronchiectasis with emphysema) in whom pulmonary function was maintained without deterioration for many years and in whom heart failure did not develop relatively unaltered renal clearance was maintained Development of heart failure in 1 was accompanied by considerable fall in renal plasma flow and a lesser fall in glomerular filtration rate compared with values obtained 2 years before Three patients with chronic pulmonary disease but without heart failure studied during acute exacerbations of bronchitis and recovery had improvement in renal circulation similar to that in patients with heart failure Temporary episodes of renal ischemia probably occur in patients with chronic pulmonary disease and may precede development of congestive heart failure

► [*The principal significance of these findings appears to be that in contrast to most forms of heart failure in which renal circulatory impairment tends to be irreversible once it is established pulmonary heart failure is associated with more temporary alterations in renal hemodynamics It is of interest also that renal circulatory impairment may precede the development of other manifestations of congestive failure by long periods and that reversible renal ischemia without other manifestations of pulmonary heart failure may accompany acute exacerbations of bronchitis in patients with chronic pulmonary insufficiency*—Ed.]

Diffusing Capacity of Lungs in Patients with Mitral Stenosis Studied Postoperatively The diffusing capacity for oxygen is the number of *milliliters of oxygen diffusing* across the pulmonary membrane/minute in response to a mean difference of 1 mm Hg in partial pressure on the two sides of the membrane It is a function of the thickness physicochemical structure and area of the surface With increased

cardiac output in response to exercise the diffusing capacity approaches a maximal value probably because an increasing fraction of the total capillary bed takes part in gas exchange

Pulmonary function was studied by R L Riley C J Johns G Cohen J E Cohn D G Carroll and R H Shepard[6] (Johns Hopkins Univ) in 14 patients with mitral valvulotomy 5 55 months before Findings were related to preoperative studies previously reported Although significant incapacity had existed a number of years preoperatively about half the patients showed postoperative diffusing capacities during exercise which were within 1 standard deviation of predicted normal values for maximal diffusing capacity The other half showed moderate to severe lowering of diffusing capacity during exercise

Patients with normal diffusing capacities probably had no extensive structural changes in the pulmonary membrane 2 with very low values probably had such changes Intermediate values could not be interpreted The 6 studied preoperatively at rest showed low diffusing capacities and were improved by valvulotomy Low preoperative diffusing capacity does not contraindicate surgery

Effects of Venesection on Pulmonary and Cardiac Function in Patients with Chronic Pulmonary Emphysema and Secondary Polycythemia Data on the effects of polycythemia in chronic pulmonary emphysema are conflicting However heart failure can be prevented when combined treatment of the heart and lung disease is stressed in addition to prevention of excessive polycythemia To determine whether the benefits were due to improved ventilation and gas exchange J Howland Auchincloss Jr and John J Duggan (Univ of New York Syracuse) studied 11 men before and after venesection who had chronic obstructive pulmonary emphysema with secondary polycythemia

After venesection all lung volumes were greater including functional residual capacity residual volume and total lung capacity Total minute ventilation showed no significant differences although ventilation increased during exercise in 3 of the 4 tested Arterial oxygen content and capacity were significantly reduced after venesection No significant changes were noted in gas exchange for the group as a whole

(6) J Cl I t 35 1008 1014 S pt mb 19 6
(7) Am J Med 2 74 8 J 1957

although they may have occurred in individual instances Comparable x rays obtained in 6 shortly before and after venesection showed no change in 3 and slight improvement in 3 Subjective improvement was noted in 2 while the other 9 showed no change The acute effect of venesection was a fall in cardiac output of not less than 1 L/minute due to a higher arterial and lower mixed venous blood oxygen concentration Stroke volume decreased Mean pulmonary arterial pressure fell 8 and 17 mm Hg in 2 patients and rose 3 mm Hg in the other subject in whom it was measured

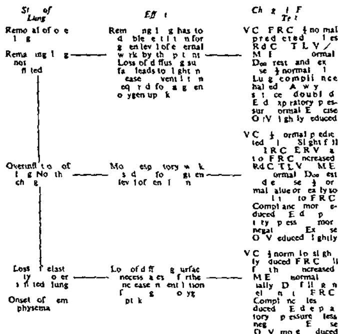
These studies show that venesection in a patient with emphysema chronic arterial hypoxia and secondary polycythemia may be followed by increased total lung capacity functional residual capacity and residual volume Probably these effects are caused by a decrease in intrathoracic blood volume Despite such changes in the volume of blood and gas in the lungs there is no evidence that the uneven distribution of ventilation and blood flow to pulmonary alveoli is appreciably altered However venesection may result in important changes in circulation with immediate reduction in right auricular pressure cardiac output and pulmonary artery pressure

The value of venesection probably lies in reduction of cardiac output right auricular pressure and pulmonary artery pressure The duration of these effects is unknown but concomitant reduction of right ventricular work may be important in therapy While venesection may be useful as an adjunct to other forms of therapy experience has shown that patients in right heart failure usually make a satisfactory recovery without venesection as long as other aspects of treatment are closely attended

Respiratory Function after Pneumonectomy After pneumonectomy without thoracoplasty the remaining lung is said to be overinflated though respiratory performance may be good M B McIlroy and D V Bates[8] (St Bartholomew s Hosp London) studied 10 patients at rest and during exercise All were men aged 39-63 and in 7 the pneumonectomy was right sided All had more dyspnea after surgery but in only 3 was this severe enough to interfere with normal activity

(8) Thorax 11 303 311 December 1956

Mean inspiratory resistance was greater than normal in each. In about half the patients the compliance of the lung was less than expected for one normal lung and decreased more rapidly than normal as lung volume increased. The compliance apparently did not decrease as the breathing rate



F g 16 — S ggested q of ch ng ft r pn umo ectomy *V C* vital capac ty *F R C* f ct onal d l eapa ity *Rd C /T L C %* res d al pac ty as pe centag f tot l pac ty *M E %* m g effic e cy pe cent *I R V /E R V* ratio f pirat serv vol m to p tory serv olume. (Court y of McIlroy M B nd L t D V Th rax 11 303 311 Dec mbe 1956)

increased indicating that the distribution of ventilation in patients with one lung remains normal. This is confirmed by normal values obtained for mixing efficiency.

Respiratory work with exercise was greater than normal even when the lung was not overinflated and greatly increased in patients with an overinflated lung. In some patients the diffusing capacity was normal for the reduced lung

volume but in others it was lower than predicted from the functional residual capacity

Absence of one lung may result in little change in the function of the other lung though some dyspnea may be noted because ventilation may need to be doubled Part of the respiratory drive may be supplied by lowered arterial oxygen tension When overinflation is present the immediate result is ventilation of the lung at an abnormally low intrathoracic pressure leading to a lung which is stiffer than normal If the lung now loses elasticity intrathoracic pressure rises functional residual capacity increases and diffusing capacity falls in relation to it (Fig 16) The only tests useful in indicating the state of the remaining lung are functional residual capacity end expiratory pressure level and comparison on exercise between the D_{CO} and the F R C

Some dyspnea is present after operation even in the absence of evidence of overinflation presumably because the remaining lung must be overventilated Overinflation accentuates dyspnea by reducing compliance Diffusing capacity is generally half that of normal persons necessitating increased ventilation for a given oxygen uptake Overinflation results in increased lung volume with low intrathoracic pressure level and normal gas diffusion Emphysema is characterized by increased lung volume with normal intrathoracic pressure level and impaired diffusion

In every patient compliance of the lung and diffusing capacity were reduced and inspiratory resistance increased In 6 with little or no overinflation of the lung or emphysema changes in pulmonary function were similar to those expected with halving of the amount of lung tissue available for respiration

► [The authors undertook this study primarily to seek answers to 3 questions (1) Does the presence of overinflation lead to dyspnea through changes in the mechanical properties of the lung? (2) Does the lowering of the diffusing capacity for carbon monoxide (D_{co}) if present have any important consequences for the patient? (3) What is the relationship or distinction between overinflation and emphysema? The answer to (1) is that overinflation is associated with an abnormally low intrathoracic pressure and so by further reducing lung compliance accentuates the dyspnea normally present after pneumonectomy The answer to (2) is that D_{co} following operation is reduced to half of normal and results in a lowered ventilation equivalent for oxygen necessitating increased ventilation for a given oxygen uptake With overinflation the respiratory work with exercise becomes considerably increased The an

swer to (3) is that the most important distinctions to be made between simple overinflation and emphysema are with respect to changes in the intrathoracic pressure level and in the diffusing capacity characterized respectively by loss of elasticity and of diffusing surface with the development of emphysema It is not clear to me whether the sequence from overinflation to emphysema is to be regarded as an inevitable progression nor whether the conclusion may be drawn that the adverse effects of overinflation are usually of sufficient magnitude to make thoracoplasty advisable following pneumonectomy in patients without pre existing emphysema Currently this is not the usual practice —Ed]

Evaluation of Clinical Significance of Clubbing in Common Lung Disorders L Cudkowicz and D G Wraith[9] (St Thomas s Hosp London) using a simple water displacement method (Fig 17) measured the end 2 cm of the fully

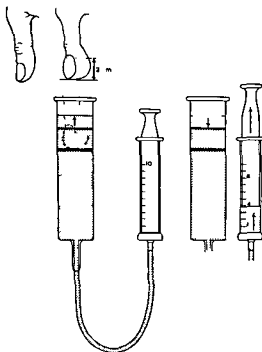


Fig 17 —P f t d fi i pl tf m i ft b t l m t d f th mb wh h d pl l m f w t 2 m h gh (C t y f C show L a d W th D G B t J T be 51 14 31 J y 1957)

(9) B t J T be 51 14 31 J n ry 1957

extended thumb in 27 patients with clubbing and compared the results with those in 50 normal controls (Fig 18) Vol umes of mass of terminal of the right thumb in 14 patients exceeded those in controls and total figures for all patients varied from 4 75 to 9 ml compared with those of controls which ranged between 3 5 and 5 75 ml

Anatomic studies of the affected fingers showed a fairly

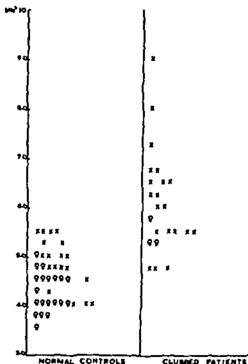


Fig 18 —Volumes of mass of terminal 2 cm of right thumb patients with clubbing and normal controls (Courtesy of C dkowcz L and Wraith D G Brit. J Tuberc 51 14 31 January 1957)

uniform abnormality but no equivalent single abnormality was found in the lung fields or cardiovascular system nor was any single clinical factor common to all patient Club bing of the fingers is an infrequent associate of common lung diseases with incidence in lung cancers about 5% and in pul monary tuberculosis less than 0 2% Left hilar neurectomy

and a ganglion blocking agent such as hexamethonium bromide did not alter shape or volume of the thumb in 2 patients

Even this small series suggests that clubbing is related to an added abnormality which occasionally complicates lung diseases Elucidation of this anomaly requires methods other than simple clinical tests It probably is localized to the pulmonary circulation because clubbing disappears after excision of small lung tumors and arteriovenous aneurysms of the lung The tumor itself is unlikely to be directly related to finger clubbing as most lung cancers are not so complicated However abnormal bronchopulmonary precapillary anastomoses near the growing tumor have been noted near lung cancers associated with painful clubbing These are probably also excised with the lung tumor which could account for amelioration of the clubbing when the tumor is resected Ablation of arteriovenous aneurysms of the lung has the same effect

Finger clubbing in lung disease points to abnormal communications between the bronchial and pulmonary arteries in at least one lung Catheterization studies have shown significantly raised arterial oxygen saturations in at least one lobar branch of abnormal lobes These patients had raised pulmonary artery pressures without heart failure or anoxia The rise in pulmonary artery pressure can be related to bilateral bronchopulmonary anastomoses In patent ductus arteriosus pulmonary artery pressure remains normal for long periods despite augmented pulmonary blood flow but often rises later in presence of raised arterial oxygen saturation in the pulmonary arteries before flow reverses through the ductus presumably due to structural changes in the smaller pulmonary arteries Occlusive change in the smaller pulmonary arteries is a mechanism which initiates formation of bronchopulmonary anastomoses and their establishment in 3 patients was on a wide enough scale to be associated with both clubbing and raised pulmonary artery pressure

► [The failure here recorded of unilateral hilar neurectomy to reverse manifestations of hypertrophic pulmonary arthropathy is at variance with the experience of Flavell (see 1956 57 YEAR BOOK p 190) who reported immediate relief of joint symptoms following vagotomy on the affected side in 5 patients —Ed]

extended thumb in 27 patients with clubbing and compared the results with those in 50 normal controls (Fig 18) Vol umes of mass of terminal of the right thumb in 14 patients exceeded those in controls and total figures for all patients varied from 4 75 to 9 ml compared with those of controls which ranged between 3 5 and 5 75 ml

Anatomic studies of the affected fingers showed a fairly

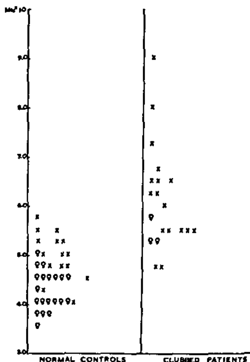


Fig 18—Vol mes of m f term al 2 cm of ght thumb in p t e ts w th l bb ng a d normal co t l (Cou tesy of C dk w c L d W th D G B t J Tube 51 14 31 Ja u ry 1957)

uniform abnormality but no equivalent single abnormality was found in the lung fields or cardiovascular system nor was any single clinical factor common to all patients Club bing of the fingers is an infrequent associate of common lung diseases with incidence in lung cancers about 5% and in pul monary tuberculosis less than 0 2% Left hilar neurectomy

dyspnea and cyanosis Administration of oxygen carbon dioxide oxygen mixtures or narcotics often converted this to complete depression of respiration and of the sensorium

These cases simulate the syndrome of intracranial hyper tension of unknown cause (pseudotumor cerebri) charac terized by increased intracranial pressure i e headaches poor vision papilledema abducens palsies and disturbed sen sorium The ventricles are normal or decreased in size Prog nosis is usually good in contrast with that of brain tumor Nothing has been found to explain the clinical picture

The pathogenesis of the increased intracranial pressure of severe pulmonary insufficiency is probably cerebral vasodi latation caused by hypercapnia Mechanical respirators with deliberate suppression of spontaneous respiration if neces sary may be a valuable adjunct to therapy

Progressive Pulmonary Dystrophy Vanishing Lung or Idiopathic Lung Atrophy L Heilmeyer and F Schmid (Freiburg Germany) present data on 4 patients aged 40 52 with complete disappearance of lung parenchyma in all or part of a lobe including the proximal portion of the bronchi and vessels in 1 cystlike cavities were also present In 3 followed roentgenographically for several years the condi tion was definitely progressive whereas in 1 it remained practically stationary for over 15 years In a fifth patient aged 56 cystlike formations which perhaps represented a less advanced stage of the process resulting in pulmonary atrophy were found

Infection of the lung or bronchi was present in all 4 pa tients at onset and seemed to be of etiologic significance In fection was also prominent throughout the course as a chronic productive bronchitis punctuated by frequent lung infections Two patients used nicotine excessively and an other the only woman in the group was employed in a cigar factory

Crenshaw concluded that disappearance of lung tissue in his cases was dependent on obliteration of bronchial and pul monary arteries on the same side and attached particular significance to the bronchial arteries In the present series extensive obliteration of the pulmonary vascular system was demonstrable roentgenologically The angiocardiogram of

( ) D tsch m d W h h 81 1 93 1297 A 17 1956

EMPHYSEMA

Pulmonary Emphysema Simulating Brain Tumor A review of 12 reported cases and 2 new cases with autopsy findings are presented by Harold O Conn James P Dunn Herbert A Newman and Gerald A Belkin[1] (New Haven Conn)

CASE 1—Woman 48 was hospitalized semicomatose after a brief history of progressively severe headaches personality changes somnolence contusion and coma suggestive of a rapidly expanding intracranial tumor Papilledema retinal hemorrhages abnormal pupillary reflexes and high cerebrospinal fluid pressure strongly supported this diagnosis She was cyanotic irrational and had tachypnea After mechanical respiration fluid therapy and pressor substances she regained normal mental state and was able to report a history of asthma for 6 7 years—i e exertional dyspnea and frequent respiratory infections—chronic productive cough ankle edema and palpitations She was discharged improved but 5 months later was readmitted in respiratory decompensation and she died Autopsy showed pulmonary emphysema with chronic bronchiolitis and focal pulmonary fibrosis hypertrophied and dilated right atrium and ventricle and evidence of increased intracranial pressure in the region of the uncus and tonsillar area of the cerebellum

CASE 2—Man 57 with dyspnea and cyanosis a long history of pulmonary emphysema with recurrent respiratory infections a series of syncopal episodes followed by headaches lethargy and confusion weight loss and weakness of the left leg was hospitalized On day of admission he was incontinent with tarry stool Comatose state convulsive episodes papilledema and increased cerebrospinal fluid pressure contributed to presumptive diagnosis of gastrointestinal neoplasm with metastases to the right hemisphere He died in the hospital Autopsy revealed extensive bullae and fibrosis pulmonary congestion and acute bronchitis No brain tumor or hematoma was present but the brain was markedly swollen with evidence of increased intracranial pressure Perivascular hemorrhages and edema were noted in the cerebellum An ulcer was found near the cardioesophageal junction

The clinical pattern is one of middle aged patients with long standing chronic bronchitis emphysema and progressive right sided heart failure culminating in acute cardiopulmonary insufficiency Some of the previously reported patients had carbon dioxide narcosis others had only extreme

(1) Am J Med 2 524 533 Ap 1 1957

vascular occlusion Presumably inflammatory infection of the lung which precedes the onset leads to sensitization of the vessels as is seen in chronic meningitis Pulmonary dystrophy would then be the result of Buerger s disease of the pulmonary and bronchial arteries The frequency of excessive use of nicotine among these patients correlates with this hypothesis which however must be confirmed histologically

The opinion held by some that pulmonary dystrophy is related to pressure caused by bullous emphysema is believed to be erroneous Two of the authors patients had normal intrapulmonary pressures Further lung atrophy developed gradually with no sharp demarcation between it and surrounding healthy tissue

The progressive course in 3 patients al o noted by others demonstrates the seriousness of the disease which eventually must result in heart and respiratory insufficiency Severe right heart deficiency was evident in the ECG of several patients In treatment emphasis should be placed on control of the accompanying infection which may account for further progression of the disease

► [The syndrome of "Vanishing Lung" is usually referred to in recent literature as bullous emphysema and is generally regarded as secondary to airway obstruction from infections and other causes The associated pulmonary vascular obliteration is most often interpreted as a consequence rather than as a cause of the condition. This suggestion that pulmonary dystrophy may be caused by an endarteritis obliterans similar to that of Buerger s disease is interesting and merits consideration as a possible pathogenic factor in those instances in which bullous emphysema develops without conspicuous antecedent bronchial infection The most striking example of an evident bronchial rather than vascular mechanism is the emphysema often associated with formation of giant bullae which develops in mucoviscidosis —Ed.] ◄

Some Physiologic Changes Associated with Surgical Excision of Emphysematous Bullae Excision of large bullae has been accepted practice in the past decade and many reports have indicated improvement in selected patients The criteria for selecting patients has been presence of a bronchial communication with the cysts and the extent of pulmonary emphysema in the remaining lung Reduction of arterial blood oxygen has generally been considered a contraindication Martin J FitzPatrick C Frederick Kittle T K Lin and James C Dowell[3] (Univ of Kansas) observed changes in the pulmonary and cardiovascular systems in 10 patients

(3) Am J Med 22 534 548 April 1957

the first patient revealed widespread lack of lung vessels on the right (Fig 19) The vessels in the upper and middle regions were completely lacking in the lower portion only the small branches were filled with contrast medium The trunk of the right pulmonary artery was narrowed and especially in tomograms appeared to be amputated Conversely



F g 19—A g ocard g m sh w g w d p d lack of l g v ls n ght (Court y of H lm y r L. d Schm d F D tsch m d Wch sch 81 1293 1 97 A g 17 1956)

the left pulmonary artery and its branches were dilated

It appears likely that vascular obliteration precedes atrophy of lung tissue Obliteration of a single branch of the pulmonary artery did not cause disappearance of parenchyma Hence occlusion of homolateral bronchial and pulmonary arteries *must be prerequisite for development of the dystrophic process* Fundamental pathologic anatomic investigation is urgently needed for further clarification It is suspected that inflammatory endarteritis obliterans is the cause of the

rest and those with long standing cardiopulmonary failure were definitely benefited by excision of bullae Benefits were most marked in patients with the greatest cardiopulmonary disability and were most readily apparent in restoration of abnormal cardiovascular dynamics to more normal range Pulmonary artery pressure decreased and right heart failure was alleviated Lung function was not appreciably altered

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CONGENITAL DISORDERS

Congenital Lobar Emphysema This established clinical entity is relatively rare Three cases are reported by A Holzel E Bennett and B F Vaughan[4] (Manchester England) Generally affected infants undergo an acute respiratory emergency in the neonatal period or during the first few months of life Dyspnea and cyanosis are usually recurrent and increasingly severe Wheezing and recession of the intercostal spaces and indrawing of the suprasternal area are often marked Examination suggests emphysema of one lung and radiologic examination shows increased air content of one lobe almost always the upper which herniates through the anterior mediastinum toward the opposite side Early recognition and lobectomy may lead to complete recovery

In 1 patient the disease was discovered accidentally at age 4 months During a 5 year follow up health has remained good without operation Another patient had such severe hypoxia that the presenting complaint was convulsions Some degree of respiratory disability persisted postoperatively In the third improvement was continuous after operation The bronchial ramifications of the removed lobe had almost no cartilage

Despite the varied clinical manifestations of the disease the radiologic appearances were similar (1) emphysema of an upper lobe (2) collapse of a lower lobe on the ipsilateral side and (3) considerable mediastinal shift away from the lesion and anterior mediastinal herniation

(4) A b D Ch ldhood 31 162 1 J 1956

with chronic generalized emphysema after surgical excision of localized bullae

A bulla typically seen in patients with pulmonary emphysema is thought to result from the rupture of a dilated alveolus into adjoining alveoli forming a larger space or air sac anatomically connected to the bronchial tree This differs from a bleb caused by the rupture of an alveolus into interstitial tissue with resultant dissection of the visceral pleura from underlying alveoli

Three men had dyspnea without anoxia or pulmonary artery hypertension All 3 had bilateral bullae of the upper lobes when first seen Pulmonary function studies closely approached normal Some slight symptomatic improvement resulted from surgery and compressed segments re expanded to fill space previously occupied by the air sac but total ventilation did not change

Three patients (1 woman) had pulmonary insufficiency hypoxia and pulmonary arterial hypertension but no cardiac decompensation Two were unable to work and were more or less permanently hospitalized One showed over all improvement in cardiovascular studies Pulmonary ventilation was reduced but time volume relation became more normal correlating well with relief from dyspnea Another was also rehabilitated and could work again emphysema remained severe and hypoxia unchanged but polycythemia and cor pulmonale were gradually developing though surgery had increased lung function and slowed the rate of progression of cardiopulmonary disability

Four men with the severest symptoms of all 10 patients had pulmonary insufficiency with hypoxia and cardiac failure 3 were in irreversible failure at the time of study and surgery The 1 operative death was in this group Surgery produced striking benefits with disappearance of congestive failure lowered pulmonary vascular pressure and resistance and increased cardiac output The underlying pulmonary problem remained unchanged but activity was resumed

Surgical excision of noncommunicating bullae in younger patients leads to little if any objective benefit Their subjective symptoms are associated with the underlying pulmonary problem Nonsurgical therapy offers more promise of relief from symptoms in these patients Patients with hypoxia at

Where one or more pulmonary veins drain into the right atrium producing signs of right heart failure lobectomy or pneumonectomy might relieve the right heart of the additional load of oxygenated blood (2) It might be possible to transplant the pulmonary vein into the left atrium or into a normally draining pulmonary vein (3) If the left superior vena cava drained into the left atrium ligation might be considered but only after careful search for additional abnormalities

CASE 1—Man 25 had a murmur since birth For several months before admission he had slight ankle swelling and breathlessness on heavy exertion He had no cyanosis or clubbing He had a harsh systolic murmur at the apex and a loud systolic murmur at the base An ECG showed right bundle branch block Catheterization showed that the right pulmonary veins entered the right atrium a concomitant aorta pulmonary communication and pulmonary stenosis

CASE 2—Girl 19 had pulmonary veins joining a persistent left superior vena cava draining to the right atrium via the coronary sinus and connected to the right superior vena cava She had aortic coarctation and patent ductus arteriosus Although she was not seriously disabled prognosis was poor

CASE 3—Girl 14 had pulmonary veins entering a dilated right superior vena cava coarctation of the aorta and a patent ductus She was undersized and activity was impaired

CASE 4—Girl 10 cyanotic from birth had been limited in activities becau e of dyspnea She was normal in stature and development but had cyanosis of hands face and limbs at rest The toes were clubbed but not the fingers Radial pulses were poor and blood pressure was not obtainable Femoral pulses were palpable The heart was enlarged and she had tachycardia with a gallop rhythm and systolic murmur and hepatomegaly An ECG showed right ventricular hypertrophy

A posteroanterior x ray revealed a right superior vena cava and a similar shadow below the left sternoclavicular joint suggestive of a left superior vena cava (Fig 20) Angiocardiography outlined tributaries of the subclavian vein but gave no evidence of a left innominate vein joining the superior vena cava (Fig 21) Cardiac catheterization via the left median basilic vein was unsuccessful The catheter did not pass beyond the subclavian vein and she died during the procedure Apparently spasm was produced closing the left superior vena cava with diminished filling and output of the left heart which was thus unable to supply the brain under sufficient pressure through the hypoplastic aorta

At autopsy (Fig 22) the right subclavian and jugular veins were seen to join a right vena cava which entered the right auricle The left subclavian and jugular veins formed a left superior vena cava which entered the l ft auricle There was no communicating innominate vein no valvular stenosis or significant septal defect

Anomalous Pulmonary and Systemic Venous Drainage *With the current improved diagnostic methods* these venous abnormalities are more easily recognized They are of three general types involving (1) the systemic veins alone (2) the pulmonary veins alone or (3) both with associated pulmonary systemic communications A A Fitzgerald Peel K Blum J C C Kelly and T Semple[5] (Glasgow) present 6 illustrative cases encountered in 6 months

A persistent left superior vena cava can usually be suspected from careful examination of the posteroanterior x ray It usually enters the right atrium and if it receives *no pulmonary drainage is of only academic interest* Frequently however it receives pulmonary venous drainage providing an arteriovenous shunt Catheterization in patients with a left superior vena cava may be difficult because of obstruction at the junction of the subclavian and jugular veins where they cross the first rib The attempt can be dangerous if the left superior vena cava enters the left atrium especially if there is coarctation or hypoplasia of the aorta

Anomalous pulmonary venous drainage can sometimes be suspected by noting unusual dilatation of the superior vena cava *in the x ray by the presence of a left superior vena* cava or by shadows curving down along the left or right heart border When it is suspected catheter blood samples should be obtained from the subclavian vein and from the superior vena cava which has significantly higher oxygen content This pulmonary systemic communication makes it difficult to diagnose a concomitant intracardiac shunt (because oxygenated blood is already present) unless the catheter enters a septal defect or patent ductus Anomalous pulmonary drainage into the right atrium via a left superior vena cava in the absence of a communication with the right superior vena cava could mimic an atrial septal defect in blood oxygen figures

Pulmonary venous drainage to the right heart systemic venous drainage to the left heart and transposition may mask the cardinal physical sign of infantile coarctation with a patent ductus i e cyanosis confined to the lower trunk and limbs

There are three possibilities for surgical correction (1)

(5) Thorax 11 119 134 June 1956

The pulmonary veins entered the left auricle normally The left auricle and ventricle were small and thick walled The aorta was hypoplastic, no larger than a normal femoral artery but it widened considerably after entry of the patent ductus arteriosus

CASE 5—Boy 15 had a persistent left superior vena cava draining into the right atrium through the coronary sinus and connected to the right superior vena cava Pulmonary venous drainage was normal There was partial transposition of the great vessels

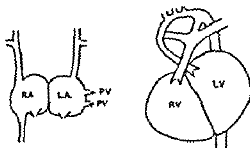


Fig 2 —Left superior vena ... left au ... hypoplastic aorta ... patent ductus arteriosus (Court y I Peel A A F ... Thorax 11 119 134 Jun 1956)

with patent ductus arteriosus He was undersized breathless on exertion and slightly cyanotic but had normal colored feet and toes

CASE 6—Boy 18 had left pulmonary veins entering a left superior vena cava which drained into the right atrium An atrial septal defect was suspected but not proved He was symptom free

Multiple Small Arteriovenous Fistulas of Lungs Since the first correct clinical diagnosis of arteriovenous fistula of the lungs was made over 100 cases have been described all related to Rendu Osler Weber disease or hereditary hemorrhagic telangiectasia Interest has been focused on large fistulas and only 7 cases have been reported in which the classic triad of cyanosis digital clubbing and polycythemia resulted from presence of multiple small pulmonary lesions in absence of any large lesion of the saccular type Two cases are reported by Milton R Hales[6] (Univ of Southern California)

In neither was the correct diagnosis established definitely during the patient s life In the first the clinical diagnosis was congenital heart disease In the second the diagnosis was made clinically but could not be confirmed

(6) Am. J P th. 32 9 7 943 5 pt Oct. 1956





F g 0 (t p) —Post roante or view show g gl b l g os ly e la g d h a t. R ght super r ena ca a is cle ly v bl an] c pond g h d w n left is probably pers tent l ft s pe fo ve Left a t rior obl q v w h wed en largem nt of r ght ve t icl d s iall hypopla t rt
F g 21 (bottom) —A g oc d ogram t 4 second sh wi g fill g of right atr m and ventricle a d pulmon y t ry Collat al n ll a d oot of n k h been nt red by dy , but non i en ent g l ft m t v in
(Courtesy of P l A A I *et l* Thor x 11 119 134 J 1956)

CASE 1—Boy 17 was hospitalized for the first time 5 hours before death after diagnosis of purulent meningitis had been made elsewhere Since age 8 he had had frequent nosebleeds Cyanosis and dyspnea appeared during the 10th year and persisted. The digits became clubbed and episodes of fainting occurred. No lesions were noted which could be interpreted as telangiectasias and no other members of the family were known to have such lesions or to have had epistaxis hemoptysis or melena Physical examination revealed typical signs of acute meningitis with petechiae The heart was believed to be enlarged and a loud systolic murmur was heard over the entire precordium The nail bed were cyanotic and the digits clubbed At autopsy no congenital abnormalities were found in the heart or great vessels The lung surfaces showed numerous tiny round red subpleural lesions resembling petechial hemorrhages (Fig 23) Close examination revealed them to be plexuses of tiny vessels Bronchovascular corrosion casts showed each lung to be studded with several hundred discrete plexu es of tiny vessels (Fig 24)

CASE 2—Woman 30 had recurrent jaundice at age 18 followed by anemia. At age 23 an enlarged spleen was removed Several episodes of coma each lasting several days followed Hypothyroidism was present Clubbed digits cyanosis and polycythemia were noted first at age 27 Extensive investigations were made during the next 3 years including cardiac catheterization angiograms and studies of pulmonary function but no abnormalities were revealed Arterial oxygen saturation remained consistently at 70 80% Because a questionable bruit was heard left thoracotomy was done but no arteriovenous fistulas were found nor did random biopsies reveal any lesions suggestive of these fistulas Liver function deteriorated and death followed 10 months later

During the last 3 years spider angiomas were noted frequently on the skin No cutaneous lesions of the Rendu Osler Weber type were seen but a discrete hemangioma was noted on the lower lip Epistaxis occurred with several upper respiratory infections and slight diffuse telangiectasia of the nasopharyngeal mucous membrane There was no history of gastrointestinal or pulmonary hemorrhage

At autopsy no congenital abnormaliti s of the heart or great vessels were revealed but small discrete vascular lesions and arteriovenous fistulas were found in lung casts

► [It is to be noted that in the few cases diagnosed antemortem the angiograms have rarely demonstrated the lesions Random lung biopsies as in the second case here reported also may fail This case however was correctly diagnosed by cardiac catheterization and pulmonary function studies Drs. Apthorp and Bates (see following abstract) report another case diagnosed clir cally and confirmed by detailed physiologic studies —Ed.]

Report of a Case of Pulmonary Telangiectasia Arteriovenous aneurysms in the lung are histologically identical with the cutaneous lesions of familial hemorrhagic telangiectasia

F g 3 (t p) —Pl r l s f c of left lower l b d l g la Blood h be wa hed t f m st of pl b t se e al ar t ll v bl s r d f i whe e d k p gm t cent t d red d f om ×1 25

F g 24 (bottom) —Pleu l f of b ch c l os o a t t dd d w th n ous pl of t y sels con t g d l ted p ph l arter a d v ns r d d f m ×3 A ow p t t l g l s i th fi ld

(Court sy of Hal M R Am J Path 32 0 7 943 Sept O t 1956)

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F g 23 (t p) —Ple ral f of l ft l wer lob a d l g l Blood h be w h d o t f m t f pl b t al st ll s ble a d foci whe e d k p gm t o cent t d d e d f m ×125

F g 24 (bott m) —Pleu l f f b cho cula e os o t t dd d w th e ou pl u s of t y ve s l t g d l ted pe ph al rt a d ve r d d f om ×3 A ow po t t l ge les th s f ld

(Cou te y of H les M R. Am J P th 32 0 7 943 Sept Oct 1956)

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are part of a widespread vascular abnormality and may cause central *cyanosis and polycythemia Criterion for diagnosis* is demonstration by angiocardiography G H Apthorp and D V Bates[7] (St Bartholomew s Hosp London) report the fifth case recorded in the literature of pulmonary telangiec tasia causing central cyanosis and polycythemia Diagnosis was suggested by findings at cardiac catheterization and pulmonary function tests

Boy 18 with cyanosis of tongue and lips for 3 years recurrent severe nosebleeds and 2 large hematemeses had no symptoms of respiratory disease or cardiac failure A year before investigation had revealed polycythemia but tomography and angiography were normal esophageal varices were demonstrated by barium swallow *At splenectomy done 3 months later for persistent thrombocytope*

TABLE 1—RESULTS OF CARDIAC CATHETERIZATION*

	SYSTOLIC AND DI STOLIC PRESSU E (MM HG)	MEAN PRESSURE (MM HG)	OXYGEN CONTENT (VOL %)
Pulmonary capillary	5/—3	2	—
artery	10/0	4	14 5
Right ventricle	25/0	5	14 6
atrium	—	—3	14 3
Superior vena cava	—	—	14.3
Femoral artery	120/70	90	16 6

Arte l saturati n=81% during catheter zat on

nia the spleen was congested and portal pressure was 255 mm sa line Liver biopsy showed grossly dilated portal venules consistent with hemangiomas

On hospitalization he had cyanosis of lips and tongue severe clubbing and cyanosis of fingers and toes dilated venules in the skin and 2 pin sized hemangiomas on the neck and thumb At examina tion the lungs were normal A soft murmur was heard loudest in systole running through the second sound and ending in mid diastole best heard at the pulmonary area and over the left lung root posteriorly Leaning forward and the Mueller maneuver inten sified the murmur which was unaffected by the Valsalva maneuver

He had secondary polycythemia X ray of the chest with tomog raphy was normal except for right ventricular enlargement. The ECG showed right ventricular hypertrophy Cardiac catheterization (Table 1) revealed lower pressures in the right side of the heart compared with those in the left excluding a right to left shunt An giocardiography disclosed an abnormal vascular pattern suggestive

(7) Thorax 12 65 67 March 1957

of dilated venous sinuses Pulmonary function tests (Table 2) showed normal ventilation no increased stiffness a larger functional residual capacity than expected and decreased diffusing capacity Arterial saturation rose to 99% when 100% oxygen was breathed but not with exercise indicating that with the increased

TABLE 2—PULMONARY FUNCTION TESTS

Height	5 ft. 10 in
Weight	122 lb
Vital capacity	3 26 L
Inspiratory capacity	1 91 L.
Expiratory reserve volume	1 35 L
Functional residual capacity	3 89 L
Helium mixing efficiency	81%
Tidal volume	0 866 L
Respiration rate	10/min.

At Rest

Arterial oxygen saturation (arterial puncture)=91%
Capacity=20 0 vol. %
Diffusing capacity of lungs (D_{co})=10 1 ml CO/min./mm Hg
Coefficient of elastic resistance=9 8 cm H O/L.

Exercise at 3 m p.h on the flat (treadmill)

No dyspnea or discomfort
Ventilation=31 L./min respiration rate=25/min.
D_{co}=11 1 ml CO/min./mm. Hg
Coefficient of elastic resistance=7 7 cm. H O/L.
Oxygen uptake 0 85 L./min.
Ventilation equivalent (O /V)=2 74

At rest on Nov 2 1955

Arterial saturation by oximeter=90%
Switch to breathe 100% O =saturation 96% in 20 sec
99% in 60 sec
Switch back to air =saturation 98% 1 ½ min. later
96% after 2 min
93% after 4 min

Exercise (treadmill)

2 m.p h at grade of 1 in 5.2=slight dyspnea only
Arterial saturation by oximeter=86% while on air
At end of exercise took 4 min to return to 92% pulse still 120 after 3 min. rest
Second study at same rate of exercise. Saturation breathing air was again 85%=switch to 100% O then 89% in 10 sec. 94% in 2 min.
Highest level that could be reached was 95% on exercise on 100% O
Ventilation breathing air=39 L./min.
Breathing O =35 L /min

blood flow in the lungs during exercise blood was passing through that could not be oxygenated even by 100% oxygen.

This unusual combination of results can be satisfactorily explained only by blood passing through greatly widened lung capillaries in which part of it does not become fully

saturated Cardiac catheterization excluded a cardiac cause of central cyanosis

Pulmonary Roentgen Findings in Familial Dysautonomia In 1949 a new syndrome in children, characterized by numerous manifestations of autonomic dysfunction was described The principal and almost constant features include defective lacrimation erythematous skin blotching excessive perspiration drooling emotional instability motor incoordination hyporeflexia and relative indifference to pain Other features which may be present include hypertension cyclic vomiting frequent pulmonary infection unexplained fever breath holding spells urinary frequency mental re-



F g 5 (left) —P umo t t root f right l g exte d g t upp r and low lobes Emphy m t us r ght pper l be p ot ud nt p o m d t num B th l g mphysemat

F g 26 (ght) —At l t t o p umon t of r ght pp lobe w th d ffu e int r stit l infilt at on nto b th l gs

(C t y f M eley J E nd Molosh k R E J Mt S Ho p 3 306 317 May Ju e 1956)

tardation convulsions and corneal ulcerations All patients have been Jewish and family histories indicate that the condition may be transmitted as a mendelian recessive

John E Moseley and Ralph E Moloshok[8] report 5 cases The pulmonary x ray findings are like those in fibrocystic disease of the pancreas Varying degrees of obstruction probably due to thick bronchial secretions lead to interstitial infiltration atelectasis and emphysema (Figs 25 and 26) Bronchial obstruction in fibrocystic disease apparently is primarily due to difficulty in removing viscid secretions A similar mechanism may be involved in dysautonomia

(8) J Mt S H p 23 306 317 M y J 1956

Atelectasis of the right upper lobe has been stressed as characteristic of pancreatic fibrosis and is also common in dysautonomia Emphysema may be less common in dysautonomia or more temporary than in fibrocystic disease The changes in dysautonomia may also resemble those described in agammaglobulinemia and some phases of idiopathic pulmonary hemosiderosis Clinical and laboratory features however distinguish them from dysautonomia From x ray findings alone dysautonomia is difficult to differentiate from aspiration or chronic interstitial pneumonia

Roentgen Manifestations of Pulmonary Hypertension in Congenital Heart Disease are described by Theodore E Keats Van Allen Kreis and Ellen Simpson[9] (Univ of California) At present cardiac catheterization is the only method by which pulmonary hypertension can be quantitatively demonstrated Chest films of 36 patients with congenital heart disease and pulmonary hypertension and of 15 with congenital heart disease but with normal pulmonary artery pressures were reviewed

Cyanosis was found in one third of the patients with pulmonary hypertension and was not related to severity of the latter Polycythemia also occurred in a third Most of those who were polycythemic were also cyanotic Cardiac enlargement was present in 83% of those with pulmonary hypertension Right ventricular enlargement was noted by x ray in 83% of the patients with and 73% of those without pulmonary hypertension No correlation between degree of right ventricular enlargement and hypertension was found Main pulmonary artery enlargement occurred in 92% of patients with pulmonary hypertension but also in more than two thirds of those without hypertension Size of perihilar vessels was not significant There was no consistent relation between Kerley s lines (Figs 27 and 28) and pulmonary hypertension nor between pulmonary vein size and hypertension

Disparity between proximal and peripheral pulmonary vessel size was the only useful roentgen criterion for pulmonary hypertension in congenital heart disease When present this finding was noticeably striking (Figs 29

(9) Radiology 66 693 700 May 1956

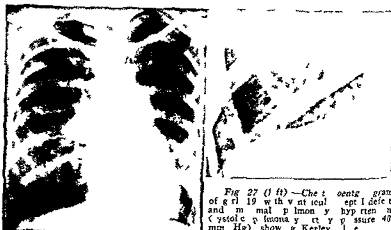


Fig 27 (l ft) —Che t oentg gram of g rl 19 w th v nt icul ept l defe t and m mal p lmon y hyp rten n (ystol c p lmona y rt y p ssure 40 mm Hg) show g Kerley l e

F g 28 (t) —E la ged prod c t on of ght l wer lung field f me pat nt showing Ke l y s l n o toph c a gle

(Court sy of Ke t T E *et al* R d ol gy 66 693 700 M y 1956)



F g 9 (left) —Ch t o tge og am f ma 34 w th t l r pt l def ct *ad pulmon ry hypertension (sy t l c p lmo ry art y p e su e 101 mm Hg) show* g d pa ty b tw p x m l d p ph l p lmon y t y

F g 30 (ght) —Ch t tg g m f b y 7 w th at l s pt l defe t w th out pulmo y h pertens on show ng p m n nt h la and p r phe l v ssels w th t d pa ty n s

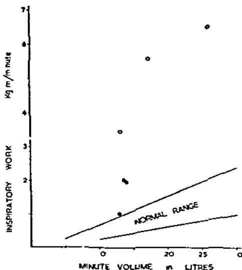
(Co rt y of Keat T E *et l* R d l gy 66 693 700 May 1956)

and 30) *It is a reliable sign only if the difference is un* equivocal and if the caliber decreases abruptly usually adja cent to the dilated hilar portion of the artery rather than the gradual diminution which is a normal variant

ASTHMA BRONCHITIS AND BRONCHIECTASIS

Mechanical Properties of Lungs in Asthma. Maximal breathing capacity and vital capacity are reduced in asthma. M B McIlroy and R Marshall[1] (St Bartholomew s Hosp London) studied the changes induced by various drugs

Mechanical work done on the lungs during inspiration



F g 31—I spiratory w k plotted gainst minut volume in 9 asthmatic patients Th sol d ci les indicat asthma t rest, d outlin circles, asthma during exercise. (Courtesy f M Ilroy M B d M rshall, R. Clin. Sc. 15 345-351 M y 1956.)

was plotted against minute volume respired in 9 asthmatic patients and compared with young normal subjects (Fig 31) Inspiratory nonelastic resistance and coefficient of elastic resistance were greater than normal before and after treatment with epinephrine bronchodilators histamine or cortisone Response to treatment varied among patients and generally reflected the clinical improvement

In asthma the mechanical properties of the lungs are abnormal in two ways resistance to air flow and coefficient

(1) Clin. Sc 15 345-351 M y 1956.

of elastic resistance are increased The latter indicates that the lungs are stiffer than normal and corresponds to reduction in compliance reported by others These abnormalities are improved by bronchodilator drugs

Measurements of intraesophageal pressure and air flow are a more sensitive method of following mechanical properties of the lung than are vital capacity and maximal breathing capacity By these methods a change in mechanical properties of lung can be measured even in normal subjects after histamine aerosol

Alpha[(Alpha Methyl 3 4 Methylenedioxyphenylethyl amino) Methyl] Protocatechuyl Alcohol Hydrochloride in Bronchial Asthma This N substituted arterenol derivative (JB 251) was studied in 126 patients with severe asthma by Irving H Itkin Walter S Burrage and John W Irwin[2] (Massachusetts Gen l Hosp) with the technical assistance of Mary Gilchrist and Alice Roach For 3 months 2 5 5 mg was given orally every 6 hours In addition each patient inhaled a mist of 1 200 solution as required to control asthmatic symptoms No serious side effects were noted

At least partial relief from symptoms was obtained by 111 of the 126 13 were unrelieved by the oral medication but were relieved by the mist Oral medication induced at least partial relief in 93 In a double blind experiment in 33 inhalation of 1 200 solution JB 251 was more effective in relieving asthmatic attacks than was epinephrine 1 100 and 4 mg tablets of JB 251 were more effective than 50-mg tablets of ephedrine hydrochloride

Most oral bronchodilators introduced since 1924 have attempted merely to avoid some side actions of ephedrine In patients who do not respond to large doses of ephedrine JB 251 seems to be effective These patients are often considered for steroid therapy It may be worthwhile to try JB 251 before such patients are exposed to the danger of the miracle drugs

The only side effect of the 1 200 solution was nausea in 3 of 67 patients and the tablets produced central nervous system stimulation in 7 of 80 at all doses and in 17 of 33 at a high dose of 4 mg

Mucoid Impaction of Bronchi is reported in 8 cases by

(2) J All rgy 27 359 368 J ly 1956.



Fg 3 —Lam gram eveal d l bl k h d w f bron h fill d w th m cus. (Courte y f G ee A. E Ann Int. Med. 46 506 5 M h 1957)

Allen E Greer[3] (Oklahoma City) The underlying cause is not clear but the condition is closely associated with asthma and obstructive bronchitis Undoubtedly many episodes are short and are cleared by expectoration of plugs of mucoid material Mucoid impaction probably results from localized accumulation of inspissated mucus in bronchi of second order distal to a bifurcation

(3) A n I t Med. 46 506-52 M ch 1957



Fig 33 —Mucou mas completely fill br chu wh ch h been ope d longi tud nally (C tesy of G A. E Ann Int Med 46 506 52 M r h 1957)

Symptoms similar to those of asthma or chronic obstruc tive bronchitis are wheezing respiration dyspnea cough and often history of allergy Fever or history of pneumonia is frequently noted Hemoptysis chest pain and expectoration of mucous plugs were noted by several patients Roentgeno grams show distinctive shadows In patients without sec ondary infection the plugs cast a V shaped shadow with the vertex toward the hilum (Fig 32) and atelectasis of varying degree is present in some Those with secondary infection show ovoid peripheral shadows reaching the pleural surface If some of the plugs are expectorated an air cavity or an air fluid level in an abscess cavity may be seen As the mucus becomes liquefied or expectoration clears the pneumonitis

the bronchi remain dilated and typical bronchiectasis is seen in unusual locations

Therapy consists of antibiotics for secondary infection drugs to relieve bronchospasm and medication to promote thinning of the secretions and prevent further impaction Potassium iodide seems to be one of the most effective drugs Steroid and x ray therapy do not appear to be helpful Bronchoscopy may aid in excluding the possibility of a visible endobronchial lesion but is of no help in evacuating the plug Surgery is indicated if secondary suppuration persists hemoptysis from bronchiectasis is persistent or diagnosis cannot be made by other means Differentiation from tuberculosis carcinoma and mucoid impaction of the bronchi is important and often difficult Dissected specimens show huge bronchi and putty like brown to greenish gray mucus (Fig 33)

Man 32 was in good health except for nasal allergy and mild bronchial asthma A cough productive of mucoid casts of the bronchi developed Sputum was negative for acid fast bacteria Six months later a lesion was first reported on chest x ray and in another 6 months had increased in size Physical examination revealed only fine post tussic rales in the right posterior interscapular area Laminagrams (Fig 32) were typical of mucoid impaction in the posterior segment of the upper lobe Bronchoscopy was normal and a bronchogram revealed no bronchiectasis in the lower lobe No radiopaque material was visualized in the involved area Posterior segmental resection of the right upper lobe showed bronchiectasis with chronic granulomas typical of mucoid impaction of the bronchi (Fig 33) Recovery was uneventful

Long Term Chemotherapy in Chronic Bronchitis Infection contributes significantly to symptoms and progressive deterioration of many patients with chronic bronchitis The most important pathogenic bacteria involved are Hemophilus influenzae and the pneumococcus Chemotherapy when required should be directed against these organisms The pneumococcus is always highly sensitive to penicillin and there is seldom a relapse after such therapy Hemophilus influenzae however is extremely difficult to eradicate with any antibiotic for more than short periods once it has become established in the sputum Prevention of relapse of H influenzae infections after therapy is one of the problems in treating advanced bronchitis since each exacerbation probably adds irreparable damage to the lungs



Fig 33 —Muc us mass compl tely fills bro chus wh ch has b en opened long tud ally (Court sy of Gr A. E An I t Med 46 506 522 Mar h 1957)

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from sputum in 2 weeks in 23 One required 3-4 weeks another 5-6 and a third 12 weeks of continuous treatment before sputum became free from mucoid and H influenzae 1 failed to respond

A total of 204 relapses was observed during 306 patient months of intermittent antibacterial treatment Most were associated with reappearance of H influenzae The obvious phagocytosis of H influenzae in bronchiectatic sputa and the close association of this organism with the presence disappearance or reappearance of pus before during and after suitable antibacterial treatment was impressive In 40% relapses occurred though bacteria could not again be cultured

Noncapsulated H influenzae is most likely a pathogen and not a saprophyte of the mucous membrane of the bronchial tree and is responsible for maintaining the chronic inflammatory process in patients with bronchiectasis

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PNEUMOCONIOSIS AND OTHER INHALATION DISEASES

Chronic Bronchitis Emphysema and Bronchial Spasm in Bituminous Coal Workers Epidemiologic Study is reported by John Pemberton[6] (Harvard Univ) Chronic bronchitis is a diagnosis of exclusion There are a number of patients mainly men over age 45 in whom clearly defined respiratory disease has been excluded who have chronic or recurrent cough and sputum which later develop into emphysema Onset is usually insidious Early in its course it may be called acute bronchitis bronchiolitis tracheitis or bronchial catarrh If sputum becomes copious the disease may be erroneously termed bronchiectasis If bronchial spasm develops it may be called asthmatic bronchitis bronchial asthma or allergic bronchitis

The characteristic feature of chronic bronchitis is hypertrophy of the mucous glands and goblet cells of the bronchi and bronchioles Pulmonary emphysema generalized or focal is a distinct pathologic entity Clinical signs may be

(6) A M A A h I d t Health 13 529 544 June 1956

J Robert May and Neville C Oswald[4] (London) treated 37 patients with advanced bronchitis by oxytetracycline and tetracycline for long periods during the 6 winter months Improvement often striking was noted in 22 (59%) 4 improved on a larger dose but were unable to tolerate it 11 were unimproved About one half had side effects from the drugs but in only 2 were these severe enough to require stopping the drugs Diarrhea was the most troublesome side effect and was less often caused by tetracycline than oxytetracycline Side effects could be eliminated or reduced by changing the drug but 14 of the 37 patients still had some discomfort from their maintenance dosages

Few cultures for staphylococci were made before treatment *so baseline figures are unavailable but there was no* significant increase in the frequency with which coagulase positive staphylococci were isolated from the sputum after 4 and after 6 months treatment Four of 21 patients from whose anterior nares staphylococci were isolated also harbored them in the sputum and all strains were resistant to 10 µg/ml or more of the tetracycline drugs Therefore about one fourth of patients receiving these drugs for 6 months *will* be carriers of resistant coagulase positive *staph*ylococci although there is no information on how many patients actually acquire the organisms during treatment This therapy seems valuable in preserving reasonable health in the later stages of purulent chronic bronchitis

Significance of Hemophilus Influenzae in Bronchiectasis of Children Previous investigations have shown that H influenzae is present in as many as 63% of bronchoscopic aspirations from children with bronchiectasis *E C Allibone* P R Allison and K Zinnemann[5] (Leeds England) followed 32 children who had purulent bronchiectasis Noncapsulated H influenzae was present in bronchoscopic aspirations or sputum in each and in 19 (59%) was present in antrum washings

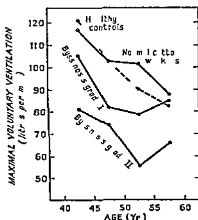
Antibiotic drugs and sulfonamides in high doses were given to 27 children and H influenzae and pus disappeared

(4) Lancet 2 814 818 Oct 20 1956
(5) Brit M J 1 1457 1460 June 23 1956

lessness cough and sputum The clinical severity of byssinosis can be accurately correlated with measurements of respiratory function (Fig 34)

Byssinosis has been overlooked and as yet unprevented because (1) the incidence of chronic bronchitis is high (2) byssinosis is often misdiagnosed as chronic bronchitis and (3) there are no specific radiographic changes

The characteristic clinical history of byssinosis is that of a worker who after some years in the industry notices tight



Fg 34 —Mea m xim l olunta y t l t on (d ect) f otton w k and healthy cont l (Co rt y f S hilh g R S F Lancet 2 261 65 A g 11 319 325 A g 18 1956)

ness in the chest Monday afternoon He may be short of breath and have difficulty walking home Monday evening After a few hours at home symptoms abate Other working days he is asymptomatic If he leaves the industry symptoms cease In some workers symptoms progress until they are present every day and an aggravating cough develops with or without sputum

Something in the dust causes either spasm or edema of the bronchioles which lessens as the week advances and reappears the following Monday The general pathology is seen best in large lung sections which show dust and emphysema The emphysema is generalized but may be more pronounced

equivocal but respiratory function tests help establish the diagnosis Bronchial spasm is a disturbance in function rather than an anatomic change The sibilant rhonchi are unmistakable The three elements are distinct and recogniz able and their development represents three stages of the disease When all are present the case is more advanced than is bronchitis alone

To determine the prevalence of chronic bronchitis emphy sema and bronchial spasm three groups of men aged 45 64 were examined There were 242 bituminous coal workers 238 industrial workers in a rural area and 131 employees of a large engineering plant in a medium sized town Chronic cough with sputum exertional dyspnea and bronchial spasm were more common in the coal miners and the high inci dence was occupational

There is no correlation between the degree of disability and radiologic evidence of pneumoconiosis The disease de pends more on the reaction of the host to inhalation of dust than on simple accumulation of dust in the lungs For this reason chronic bronchitis of coal workers might be a more appropriate name than coal worker s pneumoconio sis Pneumoconiosis in bituminous coal workers when diag nosed solely on the basis of chest x rays is not a clinical disease

When signs and symptoms of chronic respiratory disease occur in bituminous coal workers they are usually due to chronic bronchitis emphysema and bronchial spasm or less often to pulmonary tuberculosis Industrial compensation should probably be based on evidence of disability obtained from clinical examination and respiratory function tests rather than on results of x ray examination

Byssinosis in Cotton and Other Textile Workers is de scribed by R S F Schilling[7] (Univ of Manchester) Bys sinosis can be diagnosed clinically by a history of breath lessness and tightness of the chest on Mondays or on the first day at work after an absence In early stages the patient is affected only by cotton dust and there may be no sputum or cough These points differentiate byssinosis from chronic bronchitis The two are often confused in the advanced stages since symptoms are present every day with breath

(7) La cet 2 61 65 A g 11 319 325 A g 18 1956

Toxicity of Some Atmospheric Pollutants The harmful effects produced in man by contaminated fogs are well known Clinically there is respiratory distress with increased dyspnea cyanosis, progressive cardiovascular embarrassment and possibly fever and toxemia if secondary infection occurs The picture was similar in the London fogs of 1948 and 1952 in the Meuse Valley fog of 1930 and the Donora incident in 1948 The young the old and those with pre existing respiratory or cardiac disease were most seriously affected Postmortem findings were consistent with inhalation of an irritant

As no lethal fog had been adequately sampled during an incident or its chemical and physical properties determined R E Pattle and H Cullumbine[8] sampled the fog of Jan 4-6 1956 This fog was much less dense than that of 1952 Filter samples taken up to 4 20 a m Jan 5 were alkaline whereas samples taken from 9 a m until the fog dispersed on Jan 6 were acid The nature of the alkaline matter is unknown but it was probably organic The acid may have been sulfuric and was present in droplets of 10 μ mass median diameter which were far fewer than the smoke particles

The fog inhaled through the mouth produced slight tickling at the back of the throat similar to that caused by inhaling H SO_4 mist in very small concentrations Irritation was inconstant and not severe enough to cause coughing It was not present when a Siebe Gorman microfilter was worn In this fog H SO_4 mist was not a major constituent The respiratory effects produced by the fog in otherwise healthy persons could be attributed to gaseous SO alone The fog had no effect on guinea pigs exposed to it

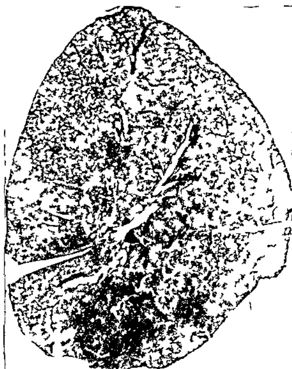
The toxic effects of smog are due to the action of small quantities of pollutants on exceptionally sensitive persons The substances are probably sulfur compounds

Clinical Manifestations of Ozone Poisoning Report of New Source of Exposure The most pronounced deleterious effect of ozone inhalation is on the respiratory system leading to pulmonary edema and hemorrhage and resulting in death if exposure is sufficiently severe or to temporary insufficiency and recovery if less severe No death has been reported *in man Secondary effects consist of irritation of the*

(8) B t M J 2 913 915 O t 20 1956

near the dust deposits (Fig 35) Histologically the bronchi show chronic inflammation and some may show metaplasia of the epithelium

Man 35 discharged fit from the army started work in the blow room at age 26 For 2 seasons he was asymptomatic but then noted unusual breathlessness during Rugby training and had to forego the



F g 35—Whole lung sect on f tton w rker w th bys n how ng g neral d emphy ma (Court y of Sch lling R. S F L ncet 2 261 265 A g 11 319 325 A g 18 1956)

games Two years later he noted that the chest was tight on Mon days at work He did not smoke had never had any chest ill nesses and no abnormalities were found

► [The difficulty of differentiating byssinosis from nonspecific bronchitis is such that the disorder most often goes unrecognized except where epi demiologic work of the kind described by Dr Schilling in this Milroy lecture is carried out Familiarity with the characteristic clinical history which as he states is the only means of diagnosis should lead to a wider recognition of the disease and to appropriate measures for its prevention —Ed.]

confined to the middle and lower zones One had no x ray changes but diagnosis was made by history

Response to all treatment was poor except potassium iodide in large doses This response to potassium iodide tended to confirm the diagnosis Further contact with hay dust was avoided Symptoms usually subsided in a month X ray changes reverted to normal by 3 months All patients were back at work in 1 3 months after first attendance at the clinic Antibiotics were not given except to 1 patient who developed a secondary bacillary infection

No relation between fungi found in the sputum and those grown from the corresponding specimen of hay was found in the cases examined There was no evidence that the same infecting agent was responsible in each case or that the organism grew in the bronchial tree Therefore the condition was probably not a true bronchomycosis It is suggested that the concentration of hay dust consisting largely of mold spores is so high in the lower respiratory tract that the terminal bronchioles literally become choked There is also probably a mild inflammatory response by bronchial epithelium

► [This form of farmer s lung' is apparently unrelated to silage gas poisoning or silo filler s disease which is caused by nitrogen dioxide from fermented corn silage but the sequelae of which have been in the past sometimes also called farmer s lung

The acute disease from toxic gases derived from silage has been recognized only recently as a distinct entity (see the following abstracts of articles by Grayson and Lowry and Schuman —Ed]

Silage Gas Poisoning Nitrogen Dioxide Pneumonia a New Disease in Agricultural Workers Two cases are reported by R R Grayson[2] (Perryville Mo)

CASE 1 —Man 66 entered an unventilated silo and was made unconscious by a yellowish brown gas present above the silage He was in the silo about 5 8 minutes before he was rescued by the patient described in case 2 lowered to the ground and given artificial respiration He recovered consciousness and appeared well but increasing dyspnea and cough developed Nine hours later he was hospitalized in severe respiratory distress cyanotic and semiconscious Temperature was 97 4 F pulse rate 140 respiratory rate 40 and blood pressure 104/70 The skin was pale clammy and wet The external jugular veins were distended the chest was emphysematous and heart tones could not be heard He had loud bubbling rales in both lung fields The white blood cell count was 25 400 Despite administration of oxygen bubbled through alcohol digitalis corti

(2) A n. I t. M d 45 393-408 Sept b 1956

mucous membranes headache and lethargy Low concentrations have a narcotizing and general depressant effect Ozone causes a decreased rate of pulmonary ventilation and lowered output of carbon dioxide

Morris Kleinfeld and Charles P Giel[9] (New York State Dept of Labor) present 3 cases of ozone poisoning in welders using a new welding technic known as consumable electrode welding Diagnosis of ozone poisoning requires a high index of suspicion, adequate occupational history familiarity with toxicologic effects and the finding of significant amounts of ozone in the working environment The presently accepted threshold limit is 0 1 ppm

Differential diagnosis includes acute pulmonary edema pulmonary infarction acute myocardial infarction bronchial asthma bronchopneumonia and pulmonary inflammatory disease due to other toxins In 2 patients clinical course was the most severe reported Marked dyspnea chest pain and cough were accompanied by only minimal chest findings Prolonged morbidity was noted in 2 patients after complete clearing roentgenographically

Treatment is symptomatic Emphasis is on prevention and control with isolation of the process and provision for adequate local exhaust ventilation

Farmer s Lung in Radnor and North Breconshire Report of 10 Cases is presented by D Ivor Williams and P P Mulhall[1] *This is an acute or subacute respiratory illness of farm* workers which develops after exposure to moldy hay An epidemic is more likely to occur early in the year when stored hay is old dusty and likely to have developed molds if incompletely dried before harvesting All patients developed the disease after exposure to dust laden air in cow houses and hay barns while hand feeding cattle All but 1 of the 10 patients in this series were seen within 4 months some in the same week and 2 the same day

Marked dyspnea on exertion developed soon after contact with moldy hay and usually had been present for several weeks Most patients had slight cough with or without expectoration *Physical signs* when present were *only fine* basal crepitations Chest x ray in 9 showed fine mottling

(9) Am J M Sc. 231 638 643 Ju e 1956
(1) B t M J 2 1216-1218 Nov 4 1956

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(2) A I t M d 45 393 408 S pt mbe 1956

sone and Levophed® he died 20 hours after admission and 29 hours after exposure to the gas Autopsy revealed acute bronchopneumonia.

CASE 2.—Man 31 was exposed to the silage gas for 2 3 minutes while rescuing the patient in case 1 He noted the gas was acrid irritating to his lungs and had the odor of ammonia He was admitted for observation about 14 hours after exposure because of

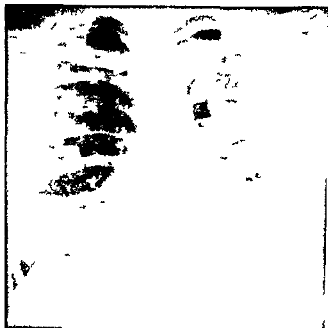


Fig 36—I filtration n l ng fi ld (Courtesy of Grayson R R A I t Med 45 393-408 S pt mb 1956)

weakness and vomiting He was not acutely ill but could not take a deep breath

Physical examination on admission showed nothing unusual 7 hours later respirations were shallow and rapid with a few inspiratory rales over the anterior portions of the chest bilaterally A chest x ray revealed diffuse patchy and confluent infiltrations throughout the middle two thirds of both lung fields (Fig 36) The white blood cell count was 12 800 He was given penicillin streptomycin and nasal oxygen and transferred to another hospital where he was admitted acutely ill and slightly cyanotic With the chest held in full inspiration respiratory excursions were limited in depth and extremely rapid There were scattered rales throughout the lungs He responded dramatically to oxygen bronchodilators and antibiotics remained afebrile and in 48 hours was clinically improved Chest film showed rapid clearing of the pneumonitis Six

months later physical examination and chest films showed no abnormalities

Gas collected from the silo contained nitrogen oxides Corn from the same silo was allowed to ferment in the laboratory and the gas produced showed mixed oxides of nitrogen Albino rats placed in proximity to the gas died

The disease produced by inhaling gases from high nitrate silage is identical with the disease described in industrial toxicology as due to fumes of nitric acid and other nitrates It is an acute chemical pneumonitis caused by the toxic action of nitrogen dioxide in the respiratory tree producing a reaction which essentially is due to nitric and nitrous acids This produces an intense inflammatory response after a latent interval of several hours The longer the exposure the more severe the pneumonia

Treatment is nonspecific and supportive Oxygen should be given Bronchodilators are indicated but are probably of minimal value If the heart is decompensated digitalis may help

Heretofore silage gas poisoning in man was thought to be due to carbon dioxide inhalation or simple asphyxia It is due to nitrogen oxides which produce chemical pneumonia and probably occurs more commonly than is recognized Physicians in rural areas should be aware of the disease during summer periods when corn is being placed in silos particularly during drought

Silo Filler s Disease —Syndrome Caused by Nitrogen Dioxide Inhalation of irritating fumes in or near freshly filled silos causes serious and potentially lethal respiratory disease in man The agent produced is nitrogen dioxide partially polymerized to nitrogen tetroxide

The term silo filler s disease designates any bronchial or pulmonary condition caused by inhalation of nitrogen oxides from fresh silage The pathologic process at autopsy varies with the amount inhaled Typical bronchiolitis fibrosa obliterans occurred in 4 men described by Thomas Lowry and Leonard M Schuman[3] (Univ of Minnesota) This is a hitherto unrecognized syndrome and important to physicians practicing in rural areas

A history of inhalation of irritating gas in or about a silo within a short time after fillin, was started is characteristic

(3) J A M A 16 153 160 S pt 15 1956

Cough and dyspnea with a sensation of choking and severe weakness are noted immediately For 2 3 weeks there is a relative remission of symptoms although some cough malaise and dyspnea remain and weakness progresses About 3 weeks after exposure the second phase begins often accompanied by chills fever more severe dyspnea cyanosis and cough unresponsiveness to usual measures leading to death or the beginning of recovery 3½ 6 weeks after exposure Numerous fine and medium moist bubbling inspiratory rales are heard over the entire extent of both lungs along with a few moist expiratory rales and sibilant asthmatic type rales during expiration X ray reveals uniform infiltration with innumerable discrete nodular densities indistinguishable from miliary tuberculosis Laboratory studies show neutrophilic leukocytosis In late stages blood carbon dioxide increases progressively All other laboratory tests are normal Autopsy in 2 cases proved a previous diagnosis of bronchiolitis fibrosa obliterans

Since exposure to the higher concentrations of silo gas or nitrogen dioxide must be rapidly fatal despite any treatment prevention is obviously the treatment of choice No one should enter a silo for any purpose from the time filling begins until 7 10 days after it is finished Good ventilation should be provided about the base of the silo during this period so toxic gases can be carried away if they develop The silo should be fenced to prevent children or animals from straying close during this danger period A blower fan should be run before anyone enters the silo

Man 28 entered a silo which had been filled the previous day He noticed an irritating odor and oppressive heat and humidity followed by coughing weakness and nausea Coughing increased progressively and wheezing was noted He became dyspneic on any exertion and was weak tired and listless Two weeks later he had chills and fever and cough and dyspnea worsened Three weeks after exposure he was treated for pneumonia but 2 days later all symptoms increased alarmingly He was hospitalized and given antibiotics and oxygen Temperature was 102 F pulse rate 128 respiratory rate 52 and blood pressure 170/80 Dyspnea was extreme and respirations were rapid shallow and gasping with frequent paroxysms of violent nonproductive cough Cyanosis was marked The expiratory phase was relatively prolonged breath sounds were reduced and numerous fine and medium moist inspiratory rales and sibilant rales of asthmatic type were heard The white blood cell count was 26 600 with 85% neutrophils sedimenta

tion rate 77 mm /hour and carbon dioxide combining power 35 mEq /L which rose during the next 4 days Chest x rays revealed innumerable nodular densities uniformly scattered throughout the lung fields

Treatment with oxygen codeine meperidine hydrochloride (Demerol®) aminophylline penicillin streptomycin and chloram phenicol (Chloromycetin®) digitalis and diuretics was ineffectual



F g 37 —Lat tag of blit t on f b on h l ong l locat on m k d by 2 f gment f m sc la t (w) ly g m d t f p l f rating fib ou ect t wh h l ov g wing d obl t t g h t ctu f rr d g l g t d d f m ×100 (C rt y f L w y T d S h m L M J A M A 16 153 160 S pt 15 1956)

The course of the disease was relentless and progressive and he died 1 month after exposure At autopsy the lungs weighed 800 and 700 Gm and contained an excess of blood and edema fluid. They were filled throughout with innumerable small discrete grossly palpable nodules which on microscopic section showed typical le sions of bronchiolitis fibrosa obliterans (Fig 37)

SARCOIDOSIS

Differential Diagnosis between Beryllium Poisoning and Sarcoidosis Miliary densities in patients without symptoms may be a manifestation of either beryllium disease or sar coidosis Definitive diagnosis is important The differential

points are reviewed by Harriet L Hardy[4] (Massachusetts Gen l Hosp)

Similarities in the two diseases are striking With variation in onset patients with either disease complain of increasing fatigue weakness anorexia weight loss dyspnea chest pain and cough At some stage examination may reveal clubbed fingers enlarged liver or spleen abnormal auscultatory findings pneumothorax emphysema or right heart enlargement with or without failure A variety of skin lesions may occur in both diseases and both may show disturbed liver function increased serum protein and globulin and occasional hypercalcemia and hypercalciuria Both may cause renal calculi

A long illness with remission and exacerbation may characterize either chronic beryllium poisoning or sarcoidosis *Death is usually due to myocardial failure or overwhelming* loss of functioning lung tissue with or without pneumothorax due to rupture of emphysematous bullae Pulmonary function studies in both diseases show defective gaseous exchange across the alveolar membrane with loss of elasticity in severe cases In both the pathologic process consists of granuloma formation with subsequent replacement of granulomas by nonfunctioning fibrous tissue

A registry has been set up at the Massachusetts General Hospital and thus far 500 cases of beryllium disease have been studied No ocular lesions have occurred None of the patients had hilar adenopathy without densities in the lung field Cervical or axillary adenopathy was rare Patients with sarcoidosis may recover completely but no patient with berylliosis has recovered The use of steroids has changed the outlook for patients with beryllium disease but has resulted in no true cures The patients are more comfortable on adequate doses of these drugs

Skin testing must be done in every case of suspected beryllium disease or sarcoidosis to exclude histoplasmosis and coccidioidomycosis Patients with sarcoidosis characteristically have depressed reactivity to several usually antigenic materials including tuberculin In contrast patients with beryllium disease respond to the same degree as does the general population Experience with a positive Nickerson Kveim reaction as evidence of sarcoidosis has not been

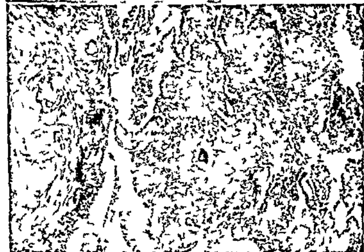
(4) Am Rev Tuberc 74 885 896 December 1956



F g 38 (left) —Chest oent g g am ot fl r scent l mp m ufa tur g w rk w th d g s f m l y tube cul s the B eck sa d nd finally be yll m d se.

F g 39 (b l w) —Ph tom graph of lung biop y f sam p t e t

(C rte y of H dy H L Am R v Tub c 74 885-896 Dec mbe 1956)



uniform In a few ca es of beryllium disease in which this test was tried the response was considered a nonspecific foreign body reaction Skin testing may provide suggestive but not final negative or positive evidence in making a differential diagnosis between the two diseases

The chest film usually raises the question of and confusion between the two diseases (Figs 38 and 39) In each case miliary tuberculosis Hodgkin s disease fungous infections carcinomatosis erythema nodosum siderosis and silicosis

must be considered Less likely possibilities are eosinophilic pneumonia or hemosiderosis

Sarcoidosis is differentiated from beryllium disease by the *presence of beryllium in granulomatous lesions in the latter* Chest x ray and histologic changes are insufficient as criteria for a correct differential diagnosis Occupational history clinical course chest x ray and biochemical abnormalities are important but the diagnosis is established only by finding beryllium in involved tissue Sarcoidosis is thus a diagnosis by exclusion

Identification of Bacterial Residues in Sarcoid Lesions Failure to demonstrate tubercle bacilli in sarcoid lesions has

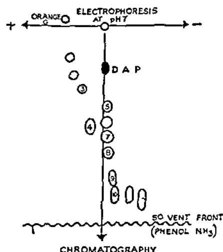


Fig 40 —Chromatophoretogram of protein hydrolysate of lymph node DAP diaminopimelic acid 1 cystic acid 2 aspartic acid 3 glutamic acid 4 dibromotyrosine 5 serine 6 glycine 7 threonine 8 alanine 9 valine 10 leucine 11 arginine 12 lysine (Courtesy of Nethercott, S E and Strawbridge W G Lancet 2 1132 1134 December 1956)

been the major objection to regarding sarcoidosis as a manifestation of tuberculosis S E Nethercott and W G Strawbridge[5] (Welsh Nat l School of Med) found α ϵ diaminopimelic acid (D A P) and mycolic acid in typical sarcoid lesions These residues are not present normally in mammalian tissue but occur in certain species and genera of bacteria including Mycobacterium tuberculosis

(5) Lancet 2 113 1134 December 1956

An electrophoretochromatogram was obtained from the sarcoid lesions of 4 patients Each revealed D A P (Fig 40) together with large amounts of aspartic and glutamic acids All three substances are known to be present in various species of bacteria including the mycobacteria Mycolic acid was also demonstrated in these lesions This acid cannot be a degradation product of human tissue because the molecule is larger than that of any fatty acid normally found in the body Similarly D A P is not a normal constituent of the body

Therefore it seems likely that at one stage a tuberculous process occurred in the lesions and that sarcoidosis may be a manifestation of tuberculosis The results of these investigations strongly suggest that the sarcoid lesions were previously tuberculous

Tuberculin Negative Tuberculosis Presenting as Sarcoidosis is reported by A W Lees[6] (Glasgow) Some cases of sarcoidosis are due to tuberculous infection Antituberculous drugs should be administered promptly in all cases

Man 26 had a cough with occasional slight sputum and dyspnea on exertion for 5-6 weeks There was no abnormality in the respiratory system no palpable lymph node and no clubbing of the fingers Temperature and pulse were normal A chest film revealed miliary opacities in the lung fields associated with gross bilateral hilar adenopathy The Mantoux t st was negative in both strengths of old tub rculin and also negative in the patient s 10 month old baby The wife s chest x ray was normal

I ronchoscopy showed thickening of the mucosal wall and biopsy revealed two follicles composed of epithelioid cells in the submucosa with giant cells but no caseation or acid fast bacilli The sections were compatible with sarcoidosis or tuberculosis Repeated sputa examinations were negative for tubercle bacilli but one grew out in culture 6 weeks later

Burning pain in the eyes and conjunctival injection developed and became progressively more severe Laboratory studies showed nothing abnormal Two months after the original studies lung x rays showed the generalized miliary mottling to be denser but repeat Mantoux tests provoked no reaction Nevertheless tubercle bacilli were cultured from gastric washings and guinea pig inoculation with sputum induced a severe tuberculous infection with recovery of tubercle bacilli from glands spleen and lung

Isoniazid (300 mg) and PAS (20 Gm) wer given daily for 1 year and streptomycin (1 Gm) daily for 4 months Within 3 weeks resolution had begun and within 4 months a chest film showed clear lung fields and hilar shadows within normal limits The Mantoux test was positive 6 months after the original exam

(6) La t 2 656 658 S pt 29 1956

ination A Kveim test 9 months after onset of illness was negative

In this case the persistently negative tuberculin test pronounced bilateral hilar gland enlargement miliary opacities in the lung fields conjunctivitis and photophobia and histologic changes compatible with sarcoidosis would have made the diagnosis practically positive were it not for the successful culture of tubercle bacilli from the respiratory secretions

Tuberculosis may produce the features of sarcoidosis and it may be difficult to distinguish one from the other The clinician must separate the sarcoid syndrome from diseases which may resemble it and identify if possible the causal agent

► [This and the preceding paper by Nethercott and Strawbridge reflect the prevalent British view that some if not most cases of sarcoidosis are manifestations of tuberculosis This is in contrast to the almost undeviating American attitude influenced for decades by the strong conviction of Warfield Longcope that sarcoidosis is causally unrelated to tuberculosis Max Pinner for a time held the contrary view that sarcoidosis is an atypical noncaseating form of tuberculosis in anergic persons but he gained few adherents to this theory mainly because the tubercle bacillus has so rarely been demonstrated in typical lesions of sarcoid while these remain uncaseated I cannot document the statement but recall that several clinical trials in this country of isoniazid or other antituberculosis agents for treatment of sarcoidosis were reported as showing no significant benefit Lees on the contrary cites a report of good results in treatment of early cases Perhaps in view of the apparent increase in prevalence of sarcoidosis the problem of response to antituberculosis therapy can be investigated on a controlled basis While doing this and apart from the problem of etiology it might also be worthwhile to re evaluate steroid hormone therapy of sarcoidosis with *simultaneous isoniazid coverage* The prevalent reluctance to treat sarcoidosis early with adrenocorticosteroids is based in part on the belief that the disease is usually benign and in part on experiences such as that of Lovelock and Stone (see 1954 55 YEAR BOOK p 203) who noted not only that improvement after hormone therapy was variable as to extent and sometimes only temporary but also that acute tuberculosis subsequently developed in several instances The relationship of tuberculosis to sarcoidosis though not necessarily causal is intriguing not alone because of the difficulty of differentiation as in the case here reported but because of the frequency with which tuberculosis complicates sarcoidosis even without the influence of steroid hormone administration Sarcoidosis although it frequently regresses spontaneously is by no means an always benign disease but may be crippling or fatal when it progresses The development of an effectual and safe method of early treatment is therefore a matter of great importance It may be doubted however that routine antituberculosis therapy without concomitant administration of steroid hormones will prove to be an effective solution to this problem —Ed]

ADENOVIRUS RESPIRATORY INFECTIONS

Clinical and Laboratory Studies in Patients with Respiratory Disease Caused by Adenoviruses (RI APC ARD Agents) Acute febrile respiratory illnesses are a major cause of disability in civilian and military populations Recently discovered viruses are now known to have caused most of the acute respiratory diseases in military recruits including undifferentiated acute respiratory disease (ARD) nonstreptococcic exudative pharyngitis and primary atypical pneumonia unassociated with cold or streptococcus MG agglutinins Viruses of this same family have also caused epidemics or sporadic cases of pharyngoconjunctival fever and acute respiratory illness in civilians primarily children These virus agents are heterogeneous antigenically and comprise a group of distinct serotypes

H E Dascomb and M R Hilleman[7] (Walter Reed Army Inst of Res) report observations on 45 recruits with RI virus infection All showed a diagnostic rise in complement fixation antibody level against RI virus Of the 12 tested for neutralizing antibody all showed a significant rise The virus was isolated from throat washings in 11 of the patients and each isolate was identified as type 7 None of the patients showed antibodies against influenza A B and C viruses cold or streptococcus MG agglutinin Streptococci were present in the throats of a few patients but none had significant increases in antistreptolysin titer

In man infections with RI virus are not manifest as a single classic syndrome Symptoms and signs primarily in the respiratory tract are quite protean and diverse and the diversity is apparently unrelated to the severity of the symptoms The composite clinical picture is shown (Fig 41) The patients were inducted into the Army during the 3 week period before hospitalization During this time minor but obvious respiratory symptoms developed in each recruit Onset of acute illness was superimposed on the minor complaints In about two thirds onset was gradual Feverish

(7) Am J Med 21 161 174 August 1956

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(7) Am J M d. 21 161 174 A g t 1956

ness pharyngitis cough with hoarseness malaise myalgia headache asthenia and dizziness increased in severity over 2-4 days before medical care was sought One third had sud den onset of chills and fever during the 24 hours before admission

On admission the commonest clinical features were fever pharyngitis and nonproductive cough All patients were

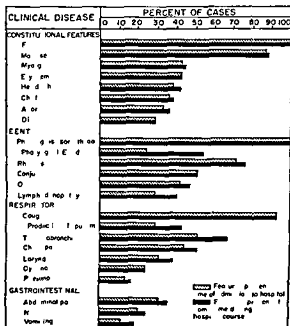


Fig 41 —Cl cal feat es in 45 cases of resp rat ry ll caused by RI v ru (Courtesy f D scomb H E nd Hilleman M R. Am J Med. 21 161 174 A gust 1956.)

acutely ill appearing listless and haggard Maximum temperatures ranged from 100 3 to 104 2 F and lasted 2 12 days

The effect of oxytetracycline was not specifically evalu ated in RI infections but clinically the drug did not influence the course of the disease The patients who did not receive the drug presented a clinical course resembling that of pa tients given the drug

Apparently many of the respiratory illnesses are caused

by viruses of the RI family (Fig 42) This includes un differentiated acute respiratory disease nonstreptococcic exudative pharyngitis bronchitis resembling atypical pneu monia and a portion of the primary atypical pneumonias in which tests for cold and streptococcus MG agglutinins re main negative Primary atypical pneumonia cases in which these tests become positive are etiologically unrelated to the RI viruses and seem to be caused by a different agent

Youth 18 had a nasal discharge and cough for 2 weeks before

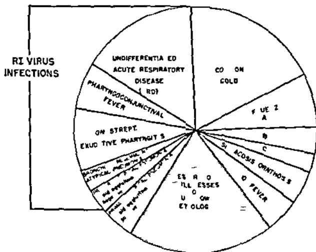


Fig 4 —Cli ical ynd mes a d et log c ent t es n ommon piratory ill esses f man. (Courtesy of Dascomb H. E. and Hilleman M R. Am. J Med. 21 161 174 Augu t 1956)

onset of an acute illness characterized by more severe cough gen eralized malaise severe headache and abdominal tenderness Tem perature was 102 F pulse rate 100 and respiratory rate 16 The exterior nares were crusted with purulent exudate and the throat was slightly erythematous Crepitant rales were audible over the right lower chest The white blood cell count was 10 800 Chest x rays were negative on admission later showed an increase in peri bronchial densities radiating inferiorly to the diaphragm and by the fifth hospital day revealed nodular but soft densities laterally at the 9th 10th posterior ribs By the fifth week the pneumonitis and ate lectasis had cleared completely

Laboratory diagnosis of type 7 RI infection was estab

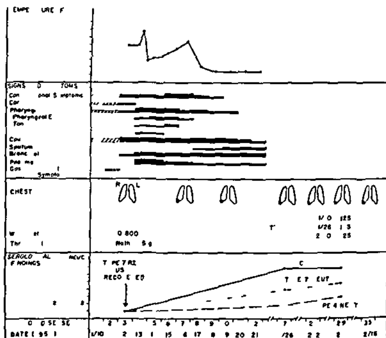


Fig 43—Data on patient with bronchial pneumonitis, atelectasis and nonstreptococcic exudative pharyngitis (Courtesy of Dingle, H. E. and Hilleman, M R Am J Med 21 161 174 August 1956)

lished by recovery of virus from throat washings and the increase in complement fixation and neutralizing antibody during the hospital course The illness represents respiratory infection which progressed from ARD to exudative pharyngitis and finally bronchitis bronchiolitis and pneumonitis with localized atelectasis (Fig 43)

Adenovirus (RI APC ARD) Vaccine for Prevention of Acute Respiratory Illness 2 Field Evaluation is reported by Reuel A Stallones Maurice R Hilleman Ross L Gauld Mildred S Warfield and Sally A Anderson[8] (Walter Reed Army Inst of Res) A new bivalent type 4 and 7 Formalin killed adenovirus vaccine prepared from infected monkey tissue culture was given by injection to about 600 army inductees

(8) J.A.M.A. 163 9 15 Jan. 5 1957

A controlled trial showed the vaccine to be effective beginning one week after initial injection causing a marked reduction in the incidence of adenovirus disease requiring hospitalization 2 through 5 weeks after vaccination (Fig 44) During this period only 1 case of serologically positive adenovirus disease necessitating hospitalization occurred in 311 vaccinated recruits in contrast to 61 cases among 313 con

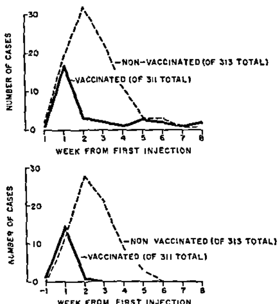


Fig 44 —In d of acut r p atory illnes ca g ho pital t v i t d a d non ac n ted g oup ll ca (top) a d ad ovi u cas o ly (b tt m) (to rt y f St llone R. A J.A.M.A. 163 9 15 J n 5 1957)

trols from the same companies a 98% reduction in expected incidence No adenovirus disease could be demonstrated in the units after the fifth week following vaccination There was also apparent reduction in the number of outpatients and in inapparent infections among those vaccinated

The vaccine is specific against adenovirus disease and appears to act antigenically by recall stimulation duration of protection is unknown The vaccine has great potential value in military populations but its role in civilian populations remains to be determined

FRIEDLANDER S PNEUMONIA ACUTE AND CHRONIC

Friedlander Bacillus Infection of Lung With Special Ref erence to Classification and Pathogenesis *Friedlander bacil lus* pneumonia is usually described as acute fulminating pneumonia affecting elderly patients with a predilection for the upper lobes of the lungs and a tendency to chronic abscess formation sequestration of the lung and even spontaneous lobectomy Men over age 40 are predominantly affected but children and infants are also stricken According to L D Erasmus[9] (Univ of Pretoria) Friedlander bacillus pneu monia should be considered an aspiration pneumonia Occa

SEGMENT OF LUNG INVOLVED IN VARIOUS TYPES OF PNEUMONIA

Figures d note number of cases

Type f pneumonia	Number f cases	A Post rior segment f upper lobe		B Apex f lower lobe		A and B		Other reas	Percentage in which areas A and or B are i volved
		Right	Left	Right	Left	Right	Left		
Primary Friedländ bacillus pneum	14	7				2		5	64
Seco dary Friedlände bacillus pn umoni	3	1						2	
N specifi ppurat pne monia	36	24	2	4				6	83
Non-suppurat e pneu moni	200	2	2	2	1	7		166	17

sionally it may be found in the lung as a secondary invader associated with other bacteria

Onset of illness was sudden in patients studied with acute primary infection and in half with secondary Friedlander bacillus infection Usual initial symptoms were fever pleu ritic pain cough and blood stained or purulent sputum About half the patients had had previous pulmonary or upper respiratory infection All patients with acute primary or sec ondary infections showed signs of segmental or broncho pneumonic consolidation and all with chronic infections had impaired percussion with crepitations over the abscess cavi ties The volume of sputum averaged 4 oz daily The sputum was yellow or green mucopurulent and in 3 patients blood streaked only 2 patients showed the classic tough brick red

(9) Quart J Med. 25 507 521 October 1956.

emulsion of blood and pus Usually the sputum resembled that of other forms of suppurative *pneumonia* The so called classic sputum is found infrequently

Although several patients were acutely ill none showed the severe fulminating form so often described and all recovered Duration of physical signs in the chest and of x ray findings was prolonged in patients with long standing pyrexia Cavitation occurred in 7 of the 17 patients requiring

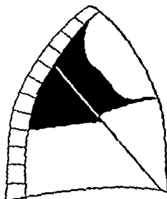


Fig 45 —Sh d d areas of l g e f om side are th s in wh ch asp ated ma al tends t lodg I den e of vol m t f the c whol n p rt s hown for v ou forms of pneumon (Cou tesy of E mus L D Q t J Med. 25 507 521 Oct ber 1956.)

surgery in 3 Spontaneous lobectomy was not noted Gross and micro copic findings in the 2 lobectomy specimens were similar to those in any kind of pneumonia except for tendency for clumps of bacteria to aggregate in the alveoli with absces formation and organization of alveolar exudate

Most patients with primary Friedlander bacillus pneumonia showed sepsis in the upper respiratory tract suggesting inhalation of infected material from this area Accepted criteria for *diagnosis of aspiration* pneumonia are *lesions in* the lung must be in areas in which aspirated material usually lodge, there must be a source of aspirated infected material and bacteriology of the sputum must resemble that of the primary lesion The distribution of lesions (Fig 45 table) showed the posterior segment of the upper lobe and apical

segment of the lower lobe to be most often affected and these areas are specifically involved when material is aspirated Incidence of upper respiratory tract sepsis was striking

Primary Friedlander bacillus pneumonia is probably a spe cific form of aspiration pneumonia with development similar to nonspecific suppurative pneumonia The infection may vary from mild to severe with gross cavitation Elderly pa tients often show a bronchopneumonic distribution of le sions thought to represent bronchogenic spread of infection in patients with an ineffective cough The same effect would be expected if the infection followed loss of consciousness Secondary Friedlander bacillus infection of the lungs prob ably develops in similar fashion resulting from aspiration of oral and pharyngeal secretions during sleep Damage to the mucoserous layers and cilia by the primary infection may allow the secondary or associated invader to become estab lished

Evaluation of 22 Patients with Acute and Chronic Pul monary Infection with Friedlander s Bacillus Typically this is a fulminating lobar pneumonia with high mortality Prog nosis has been altered since the advent of streptomycin chlortetracycline oxytetracycline and chloramphenicol but

IN VITRO SENSITIVITY TESTS ON 12 STRAINS OF FRIEDLANDER S BACILLUS*

Case	Chlortetracy lin	Oxyt tracyclin	T tracycli	Chl mphenicol	Streptomycin
1 F B	<1 0	<1 0	<1 0	<1 0	<1 0
2 F H	10 0	<1 0	<1 0	2 0	3 0
9 R M	10 0	3 0	<1 0	0	<1 0
10 R T	20 0	<1 0	2 0	10 0	2 0
11 A M	10 0	<1 0	<1 0	2 0	3 0
12 J S.	10 0	>50 0	<1 0	<1 0	<1 0
13 E W	<1 0	1 0		5 0	3 0
14 J M	4 0	2 0	2 0	2 0	5 0
15 A G	<1 0	<1 0	<1 0	3 0	3 0
16 R P	50 0	30 0		4 0	<1 0
18 C J	>50 0	>50 0	>50 0	<1 0	>30 0
21 W T	<1 0	<1 0	<1 0	3 0	5 0

Concentrat on in μg /cu mm.

it is still difficult to manage Benjamin M Limson Monroe J Romansky and James G Shea[1] (Washington D C) re evaluate the factors which contribute to the high mortality rate

(1) Ann I t Med. 44 1070-1081 J ne 1956.

Therapeutic failures are due to inherent virulence of the organism lowered host resistance lack of an effective agent against the micro-organism or delay in therapy In vitro sensitivity tests on 12 strains of Friedlander s bacillus isolated from patients (table) have shown them to be generally susceptible to chlortetracycline oxytetracycline tetracycline chloramphenicol and streptomycin

Data indicate that the antibiotics used are generally effective but other factors contribute to the poor response to therapy The tendency of patients in this economic group to delay in seeking admission to the hospital allows rapid progression and prevents early diagnosis and therapy The patients who died were all alcoholics and some had delirium tremens Lowered host resistance was obvious White blood cell counts were low and all but two had bacteremia Leukopenia and bacteremia are serious prognostic signs

In an alcoholic patient admitted with severe pulmonary infection Friedlander s pneumonia should be suspected A *gram stain of the sputum should be done immediately and* therapy directed against Friedlander s bacillus pending its identification A combination of streptomycin and one of the tetracycline group or chloramphenicol is presently the treatment of choice

PULMONARY MYCOSES

Systemic Cryptococcosis without Central Nervous System Involvement Case Report is presented by R F Wettingfeld E C H Schmidt C F Naegele and A A Doerner The clinical pattern of cryptococcosis is variable and frequently associated with other diseases Often diagnosis is not made until operation or autopsy Systemic dissemination without central nervous system involvement is rare and coexistence of tuberculosi even more rare The case reported is the first known instance of systemic cryptococcosis without central nervous system involvement but with tuberculosis and multiple sarcomatous tumor The variable clinical course of cryptococcosis with its tendency to remission chronicity and spontaneous healing of lesions makes evaluation of therapy difficult Prognosis is relatively good if the central nerv

(2) A I t M d 44 1259 1264 Jun 1956

ous system is not involved Local disease of tissue and bone has been successfully treated by incision and drainage or amputation Apparent cure of localized pulmonary disease by lobectomy has been reported

Man 60 had a severe upper respiratory infection productive cough weakness and weight loss for 1 month Chest film revealed a lesion at the right base Cryptococcus neoformans was cultured from a sinus tract leading to the right tibia The leg was amputated after other treatment failed One year later C neoformans could still be cultured from sputum and from lesions which developed on the chest A bone survey revealed osteoporosis of the right pubic *ramus and stump of the right femur Tubercle bacilli were first* found 2 years after onset of the disease The course was progressively downhill At autopsy there were disseminated tuberculosis of the lung liver and spleen cryptococcus infection of the right thorax leiomyoma of the stomach liposarcoma of the testis with metastases to the pleura and inguinal nodes and acute obstruction of the ileum due to fibrous band

Primary Pulmonary Aspergillosis Report of Unusual Case Successfully Treated by Lobectomy is presented by Felix A Hughes Robert D Gourley and James R Burwell[3] (Memphis Tenn) The fungus is widespread but primary infection in man is rare It is more common as a secondary infection in chronic pulmonary disorders

Onset is usually insidious and clinical course indistinct and chronic Manifestations are bronchitis like broncho pneumonia like or most commonly like a chronic granuloma with symptoms similar to those of tuberculosis cough night sweats low grade evening fever weight loss and hemoptysis Generalized dissemination is rare There are no typical laboratory findings other than the fungus in the sputum usually considered unimportant by the clinician The white blood cell count is not appreciably altered Occasionally eosinophilia with a count as high as 10% is noted

The radiologic picture of pulmonary aspergillosis varies but most often shows enlarged hilar shadows with radiating weblike infiltrations A rare radiologic finding reportedly pathognomonic is a solitary density with a clearly defined thin crescent shaped area of radiolucency outlining the superior limit of the mass usually in the upper lobe areas (Fig 46) The present case the tenth reported was successfully treated by lobectomy Examination of the resected specimen

(3) Ann S g 144 138 144 July 1956

Fig 46—Adm n film f lm on right enlarged 8 times to how c esc t h gh l ght (Courtesy f H gh F A t l A S g 144 138 144 July 19 6)



F g 47—A t my etoid gran le b on b l (Courtesy f H ghes F A. t l A S g 144 138 144 J ly 1356)

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(3) Ann Surg 144 138 144 J ly 1956

foci and from 95% of the cavities in the drug resistant patients whereas the corresponding figures for the drug sensitive group were 9% and 17% respectively The longer the treatment the less frequent were viable bacilli isolated from the drug sensitive group

It is impossible to test the drug resistance of tubercle ba

TABLE 1—SPUTUM POSITIVITY AND DRUG RESISTANCE RELATED TO RESULTS OF BACTERIOLOGIC EXAMINATION OF LUNG SPECIMENS

Sputum	N of patients	Type of l	N of les ns	Bacteriol gical sults		
				C lt GP +ve	Y +ve Z Y −ve Cult GP −ve	C lt GP −r
Posi nd res ta t t drugs use	11	Case focus	45 (00)	43 (96)	(2)	1 (2)
		Cav y	2 (00)	9 (95)	(5)	
Negati e nd sensiti e to drugs in use	56	Caseo focus	94 (00)	17 ( ) (9 esista t)	146 (75 /)	31 (6)
		Cavity	60 (00)	0 (7) (1 resistant)	22 (37)	8 (46)

C lt/GP=Cult r on Lowen t n Je sen m d m nd/ gu p g oculat on
Z N =C t t film t d by Z hl Ne l en

TABLE 2—EFFECT OF DURATION OF CHEMOTHERAPY ON POSITIVITY OF LESIONS

O g isms i put m	P i vity f le ions			
	Dur tion f hem ther py m ths			
	0–5½	6–1 ½	2 17½	18–23½
Drug resistant	4/ 5 (93)	37/39 (95)	7/7 (00)	4/4 (00)
Drug sensiti e	4/53 (2)	5 6 (8)	2 79 ( )	0/11

(X = 1 56 P<0 001)
F ct on p sent mb f l ons (f y type) ont g bl ga m ov tot l n mber f le o s examin d

cilli if the organisms cannot be cultured from the patient Patients who had never shown resistant organisms in their sputum and whose sputum was negative at the time the lung was examined were less likely to have viable bacilli in the

showed small clumps of fungus in some bronchioles which superficially resembled the sulfur granules of actinomycosis (Fig 47) but closer inspection revealed the filaments to be much larger and coarser

There is no specific medication for primary pulmonary aspergillosis Iodides sulfonamides arsenicals penicillin streptomycin and x ray therapy have been recommended by some but others have found them ineffective Treatment of choice in localized forms is resection Treatment of the secondary type should be directed toward the initial lesion If it is controlled the fungous infection is usually annihilated

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TUBERCULOSIS

Influence of Chemotherapy on Bacterial Content of Tuberculous Pulmonary Lesions was investigated by Sheila M Stewart F W A Turnbull and Agnes R MacGregor[4] (Univ of Edinburgh) Patients were divided into two groups depending on whether their sputum had at any time contained resistant organisms Those who had grown drug resistant organisms were found to have lesions containing viable organisms after drug therapy Such a finding was less frequent in patients whose organisms had been drug sensitive The percentage of lesions containing viable bacilli was inversely proportional to the length of chemotherapy in the drug sensitive group but no such effect was observed in the drug resistant group These findings suggest that drug resistance plays a major part in sterilization of the lesions (Tables 1 and 2)

Histologic evidence of activity of the linings of pulmonary cavities was also closely correlated to the presence of viable bacilli (Table 3) Viable bacilli usually resistant were obtained from most of the active lesions and no viable bacilli were recovered from the inactive lesions The results from the partially active lesions were intermediate but no resistant organisms were isolated from them

The main factors affecting the positivity of lesions apparently are drug resistance and duration of *effective chemotherapy* Viable bacilli were obtained from 96% of the caseous

(4) Tubercle 37 388-403 1956

therapy needed for sterilization Large cavities are more *likely to contain viable organisms than small ones* The duration of chemotherapy makes such a straight comparison of little value

The use of a combination of drugs known to prevent the emergence of drug resistant bacilli is of importance If the bacilli have become resistant it is less likely that the lesions will be sterilized If the organisms are sensitive to the drugs in use at least 12 months treatment and probably longer is necessary for complete eradication of viable bacilli

Chemotherapy can sterilize both cavities and caseous foci irrespective of their size If treatment is given for a sufficient time open healing of cavities can be achieved *Prolonged* chemotherapy may prove a satisfactory alternative to surgical *treatment in many cases of pulmonary tuberculosis*

Effect of Specific Therapy in Primary Tuberculosis of the Child is *reviewed* by Arthur Robinson and Maryethel Meyer[5] (Denver) Of 69 children studied 1 5 years 35 were aged 1 3 35 were boys Anorexia fever cough or pallor were present in 35 whereas the others had asymptomatic disease found on routine or contact examination On admission 19 had malnutrition pallor lethargy or abnormal chest findings Acid fast bacilli were found on culture of gastric washings in 15 were absent in 52 and not done in 2 All smears were negative and all patients had positive tuberculin tests

Treatment varied but all treated children received some combination of streptomycin isoniazid and para aminosalicylic acid for 9 months Results in treated children were compared with those in untreated No complications occurred in the 17 treated patients aged 1 3 years but complications occurred in 6 of the 18 untreated In the older group no difference could be demonstrated between children treated and those not treated Specific therapy apparently did not alter the clinical or roentgen course of uncomplicated primary tuberculosis The results with specific therapy in the group aged 1 3 *years warrant further investigation* of therapy in this age group

► [The pediatric terminology which refers to manifestations of progression of tuberculosis in childhood beyond the initial phase as *complications* has led to an artificial division of the problem of evaluation of

(5) J P d c 48 705 709 J ne, 1956

lung lesions than those whose organisms were resistant The persistence of positive sputum is predominantly due to drug resistance although the extent of the disease and the defenses of the patient may contribute If resistance were merely a function of the type of patient and if resistance and positivity occurred simultaneously without direct relationship between the two these patients would have been expected to fall into the resistant and positive group However they responded satisfactorily when combinations of drugs were used to which their organisms were sensitive If effective therapy alone is considered there was a good re

TABLE 3—Histologic Evidence of Activity of Linings of Pulmonary Cavities Related to Results of Bacteriologic Examination of Lesions

Histological evidence of activity	*Bacteriological results*				*Total*
	+ve and resistant	*+ve and sensitive*	*ZN +ve Cult/GP −ve*	*ZN −ve Cult GP −ve*	
Active	6	3	2	2	13
Partially active	0	4	8	6	18
Inactive	0	0	2	6	8
Total	6	7	12	14	39

Z N = Concentrated film stained by Ziehl Neelsen
Cult/GP = Culture on Lowenstein Jensen medium and/or guinea pig inoculation.

lationship between the positive isolations from the lung and duration of therapy

Viable organisms were isolated from cavities only if healing was incomplete No viable bacilli were isolated from lesions histologically inactive When the bacilli were sensitive to the drugs used many cavities showed at least partial healing The more active lesions were found in patients who had received less than 12 months chemotherapy When treatment had been continued for longer periods a number of lesions still showed some evidence of activity on pathologic examination even though viable organisms were not found This may indicate that some viable organisms cannot be isolated by standard methods but it is equally likely that evidence of activity remains for some time after viable bacilli have been eradicated

The larger the cavity the greater the duration of chemo

never received it and in 1950 52 8 cases of primary resistance were seen among 109 cultures from meningitis In 1953 none was found but sensitivity tests were performed less often In 1954 of 59 cultures from different types of primary tuberculosis only 1 was initially resistant to streptomycin In 1955 there were 3 in 100 examinations

Until 1952 resistance of bacilli to streptomycin always had a serious portent because progression of tuberculous meningitis was as rapid as in untreated patients Conversely in 4 recent cases resistance to streptomycin was an incidental finding in cultures isolated from cerebrospinal fluid the patients were treated with isoniazid PAS without streptomycin The situation is the opposite with respect to isoniazid since a few resistant strains have been isolated from patients during treatment In contrast with relative frequency of primary resistance to streptomycin the only case of initial resistance to isoniazid was in a case of bovine tuberculosis Virulence for man of bacilli resistant to isoniazid appears to be diminished but not completely abolished

Serum Isoniazid Levels and Catalase Activities of Tubercle Bacilli from Isoniazid Treated Patients Mycobacteria like other aerobic bacteria synthesize catalase which decomposes hydrogen peroxide to molecular oxygen and water In culture mediums isoniazid resistant mutants are completely or partially deficient in catalase if the amount of isoniazid in the mediums is small When the concentration of isoniazid is increased only catalase negative isoniazid resistant mutants emerge The clinical importance of catalase activity is that catalase negative mutants of tubercle bacilli are less pathogenic for experimental animals and probably for man than are catalase positive isoniazid resistant mutants

W Mandel M L Cohn W F Russell Jr and G Middlebrook[7] (Denver) correlated serum levels of active isoniazid with the catalase activities of the cultured isoniazid resistant mutants from these patients after initial treatment with isoniazid 3 5 mg /kg /day Of 56 patients studied 33 excreted catalase negative and 23 catalase positive mutants

Results (table) showed that patients who excreted catalase negative mutants generally achieved higher micro

(7) Am. J M Sc. 233 66-68 J ry 1957

specific therapy If antimicrobial therapy prevents the complications (i e any manifestations of progressive disease) is it important whether or not it conspicuously affects the speed of resolution of the primary complex? Yet much weight *seems to be given to the fact that frequently* as in the present study it does not What is more disturbing in the results here reported is that specific therapy failed to prevent complications in 2 of 17 treated children in the 3 10 age group Both of these children however received only streptomycin and PAS having been under treatment in the years before isoniazid became available The ratio of 6 cases of progression in the untreated to none in the treated children in the 1 3 age group is consistent with what may reasonably be expected of present day therapy It will be surprising if studies involving larger numbers do not confirm these results not only for the youngest but also for other age groups —Ed]

Sensitivity to Antituberculosis Drugs of Strains of Bacilli Isolated from Primary Tuberculosis in Children was studied by Henriette Noufflard Robert Debre and Simone Foussereau[6] (Paris) Since the end of 1952 no acquired resistance to streptomycin was encountered in children under treatment for primary or postprimary tuberculosis although it was relatively frequent in preceding years Four cases of resistance at outset of treatment were observed Five strains resistant to isoniazid were found among 219 cultures Four were isolated in patients treated with isoniazid Three cultures (2 from gastric lavage and 1 from cerebrospinal fluid) were isolated while patients were under treatment 1 was recovered after cessation of treatment and the fifth from a patient with glandular tuberculosis never treated with isoniazid was a strain of bovine tuberculosis which perhaps explains its reduced sensitivity A culture from 1 child isolated after 11 months treatment with isoniazid PAS was resistant to streptomycin and seemed partially though not certainly resistant to PAS All other cultures tested except 1 were sensitive to PAS

Appearance of resistance to streptomycin during treatment of acute tuberculosis in children formerly was not rare Striking disappearance of this phenomenon since 1952 apparently is explained by use of isoniazid at first given with streptomycin but since 1954 almost always only with PAS In contrast to disappearance of acquired resistance initial resistance to streptomycin is still observed but not at the rate which caused alarm in 1952 In 1949 a case of resistance to streptomycin was observed in an infant who had

(6) P e e méd 64 1791 1793 Oct 31 1956

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(7) Am. J M S 233 66 68 J n ry 1957

biologic levels of isoniazid after the test dose than did patients who excreted catalase positive mutants There was a significant relationship between rate of metabolic inactivation of isoniazid measured by 6 hour serum levels and catalase activity of the tubercle bacilli The results establish the 6-hour serum assay of isoniazid as a reliable index for estimating the concentration of active drug delivered to multiplying tubercle bacilli in vivo

Once an isoniazid resistant mutant is established, increasing the dosage does not affect the catalase activity There

MICROBIOLOGIC SERUM LEVEL OF ISONIAZID SIX HOURS AFTER 4 MG/KG DOSE

Number of patients excreting	μG INH/ML						
INH resistant organisms that have	*<04*	*04*	*06*	*08*	*12*	*16*	*>16*
No catalase activity (33)	2	1	2	2	1	6	19
Some catalase activity (23)	13	3	2	1	3	1	0

fore an effective initial dose is most important Nearly one half of patients receiving 3 5 mg/kg isoniazid daily do not achieve satisfactory microbiologically active levels

Isoniazid Susceptibility Catalase Activity and Guinea Pig Virulence of Recently Isolated Cultures of Tubercle Bacilli Sputum cultures were planted at co-operating hospitals and mailed to the Trudeau Laboratory when fully grown Subcultures were then made in liquid Tween® albumin and *American Trudeau Society solid medium Drug susceptibility* was tested by inoculation into solid egg medium containing various concentrations of streptomycin or isoniazid Virulence was tested by injection of subcultures into guinea pigs Catalase was tested by adding hydrogen peroxide to the subculture and observing oxygen bubbles

Emanuel Wolinsky Marjorie M Smith and William Steenken Jr[8] (Trudeau Found) correlated these factors in a study of 131 cultures (Table 1) and correlated catalase activity with isoniazid susceptibility in another 404 cultures (Table 2) A negative catalase test was observed only in cultures resistant to isoniazid 95% showed a high degree of resistance and 5% moderate *Catalase positive cultures* were found equally in all categories of isoniazid susceptibility

(8) Am. Rev Tuberc. 73 768-772 M y 1956.

Of 219 cultures highly resistant to isoniazid 179 were catalase negative All 200 drug susceptible or slightly resistant cultures were catalase positive

The relation between catalase activity and guinea pig virulence was clearcut Of 113 catalase positive strains 90% were virulent or only slightly attenuated In general isoniazid resistance and guinea pig virulence were inversely related

TABLE 1—CORRELATION OF ISONIAZID SUSCEPTIBILITY CATALASE ACTIVITY AND GUINEA PIG VIRULENCE OF 131 CULTURES*

ISONIAZID SUSCEPTIBILITY	CATALASE ACTIVITY	GUINEA PIG VIRULENCE			
		Virulent	Slightly Attenuated	Highly Attenuated	Avirulent
Susceptible (80)	Pos	76	4	0	0
	Neg	0	0	0	0
Slightly resistant (18)	Pos	11	4	0	3
	Neg	0	0	0	0
Moderately resistant (13)	Pos	3	2	1	3
	Neg	0	1	0	3
Highly resistant (20)	Pos	1	1	0	4
	Neg	0	2	1	11

* Figures in parentheses indicate number of cultures

TABLE 2—CORRELATION OF ISONIAZID SUSCEPTIBILITY AND CATALASE ACTIVITY OF 535 CULTURES INCLUDING 131 FROM TABLE 1

CATALASE ACTIVITY	NO CULTURES	ISONIAZID SUSCEPTIBILITY							
		Susceptible		Slightly Resistant		Moderately Resistant		Highly Resistant	
		No	%	No	%	No	%	No	%
Positive	346	98	28	102	29	106	31	40	12
Negative	189	0		0		10	5	179	95
Total		98		102		116		219	
% catalase positive		100		100		91		18	
% catalase negative		0		0		9		82	

Finding a negative catalase test in a culture of tubercle bacilli is significant It reliably indicates moderate to high isoniazid resistance and the probability of attenuation of virulence for guinea pigs All degrees of isoniazid resistance or susceptibility may be noted among catalase positive strains and their virulence for guinea pigs cannot be accurately predicted

An uncontaminated culture of acid fast bacilli which gives a strong catalase reaction should be suspected of being either a saprophyte or an atypical acid fast strain Significant numbers of catalase positive isoniazid resistant mutants emerged in at least two patients who received initial therapy with 10 mg/kg isoniazid daily

Human Infection with Yellow Acid Fast Bacillus Report of 15 Additional Cases is presented by Lawrence E Wood Victor B Buhler and Ann Pollak[9] (Kansas City Mo) Atypical acid fast organisms have been isolated occasionally from the sputum gastric washings or pleural fluid of patients with pulmonary disease Many have been saprophytes but a few have been pathogens Human disease has occurred from an atypical acid fast organism called the yellow bacillus because of its yellow appearance when grown on culture mediums This distinguishes it grossly from the cream to buff color produced by human tubercle bacilli and the orange color produced by the acid fast saprophyte The yellow bacillus produces a smooth colony is acid fast with the Ziehl Neelsen or Fite stain and is larger than the bacillus of the H37Rv strain of Mycobacterium tuberculosis It does not produce progressive fatal disease in guinea pigs but is fatal in hamsters

In 17 cases reported (2 from a previous report) the yellow bacillus was cultured in 15 and in none was a typical tubercle bacillus recovered The technic of primary isolation of these organisms was the same as that customarily used for culturing tubercle bacilli (table)

The disease produced by the yellow bacillus resembles tuberculosis clinically and roentgenographically It is usually a chronic disease which may be localized or generalized All patients with widely disseminated infection died In 10 the lesions were apparently confined to the lungs primarily the upper lobe Cavity formation was frequent One had a pleural effusion without demonstrable pulmonary parenchymal lesion 4 had involvement of at least one other organ system (genitourinary disease splenic lesion chorioretinitis and nodular skin lesions in 1 each) Three patients had generalized disease Autopsy on 1 showed massive caseation of the lymph nodes and spleen and smaller lesions in the liver

(9) Am. Re Tube c. 73 917 929 J ne, 1956

Laboratory Data from Patients Infected with Yellow Bacillus

Case Number	Age Race Sex	Present Status	Result of Tuberculin Test	Cultures [illegible] and Results	Guinea Pig Inoculation (from Cultures)
1	34 N F	Asymptomatic	+	Pleural fluid +	No progressive disease
2	50 W M	Mild symptoms is working	Not done	Sputum + gastric washings + bronchial aspirates +	No progressive disease
3	36 W M	Symptom free	− (2 days) + (5 days)	Sputum +	No progressive disease
4	53 W M	Well and working	+	Sputum +	No progressive disease
5	44 W M	Asymptomatic working full time	+	Lung surgical specimen + gastric washings +	No progressive disease
6	37 W F	Unable to follow for 10 months	+	Sputum + gastric washings +	No progressive disease
7	56 W M	Unable to follow for 8 months	+	Sputum +	No progressive disease
8	45 W F	Receiving treatment by private physician	+	Sputum + pleural fluid +	Gross evidence of disease
9	43 W F	Dead	Not done	Pleural fluid +	No progressive disease
10	39 W M	Unable to follow for several months	Not done	Sputum + gastric washings +	No progressive disease
11	63 W M	Unable to follow for 33 months	+	Sputum +	No progressive disease
12	54 W M	Unable to follow for 8 months	−	Sputum +	No progressive disease
13	55 W M	Dead	+	Sputum + lung surgical specimen +	No progressive disease
14	65 W M	Dead	Not done	Sputum + spleen surgical specimen + autopsy +	No progressive disease
15	1 W M	Dead	−	[illegible] + autopsy +	No progressive disease
16	34 W F	Dead	− first time − second time + third time	Spinal fluid +	No progressive disease
17	4 week W M	Dead	Not done	Not done	Not done

lungs gastrointestinal tract pancreas and adrenal glands The other 2 were a mother and her baby At operation for cholelithiasis the mother had peritonitis and meningitis and a miliary pulmonary infiltrate subsequently developed The baby died at age 1 month and autopsy revealed massive caseous pneumonia extensive involvement of the hilar *lymph nodes and less extensive involvement of the spleen* and liver

Tuberculin skin reactions tested on 11 patients were positive in 7 consistently negative in 2 negative on admission in 1 and positive 3 weeks later and negative in 1 at 48 72 hours but positive on the 5th day

An initial diagnosis of tuberculosis was made for all patients and they were treated accordingly Most received antimicrobial therapy consisting of some combination of streptomycin isoniazid and para aminosalicylic acid Most showed some clinical and roentgenographic improvement Those with generalized disease did not respond Six patients had excisional pulmonary surgery along with medical treatment—4 lobectomy and 2 pneumonectomy

Preliminary data indicate that the yellow bacillus is susceptible to streptomycin in therapeutic concentrations Para aminosalicylic acid only temporarily inhibits growth The effects of isoniazid are variable and most strains are resistant to it even in patients who have not received the drug In the experimental animal streptomycin treatment in doses analogous to those given humans produces prolongation of life diminution in extent of disease and reduction in number of organisms in the lesions

At present 4 of the 17 patients are well and working 1 has neither x ray nor bacteriologic evidence of disease but complains of cough 5 have been lost to follow up and 6 have died Superficially the prognosis appears gloomy but many of these patients were seen by the authors because of their severe clinical course No accurate conclusion as to ultimate prognosis can be drawn from this series Perhaps the symptoms and clinical course are actually less severe than in patients with the same degree of tuberculosis involvement

Treatment of patients infected with yellow bacillus is identical with that for tuberculosis In many cases the diag

nosis has been made only in retrospect after months or years of tuberculosis treatment

The incidence of infection by the yellow bacillus is infrequent compared with that of M tuberculosis The cases presented were found in the greater Kansas City area over a period of 5 years after studying hundreds of patients with pulmonary disease The series is too small to draw valid conclusions concerning epidemiology age sex or racial incidence

► [Whether the "yellow" acid fast bacillus should be considered as a variant strain of M tuberculosis or as a distinct species is under discussion among microbiologists Meanwhile it seems unnecessary to classify the disease here described as distinct from tuberculosis since the clinical and pathologic characteristics are essentially the same except in relation to the response to various antimicrobial agents —Ed]

ACTH and Cortisone as Adjuncts in Treatment of Advanced Pulmonary Tuberculosis Steroid hormones have been shown to be beneficial in overwhelming infections due to meningococci pneumococci salmonellae brucellae or klebsiellae but have not been used in treating severe tuberculosis Peter Elsbach and John R Edsall[1] (Bellevue Hosp N Y) report on 3 patients all with severe chronic alcoholism who had far advanced pulmonary tuberculosis not previously treated All were deteriorating rapidly and showed severe toxicity with high fever or subnormal temperatures semicoma delirium or shock in addition to respiratory distress and cyanosis None of the 3 responded to vigorous antituberculosis chemotherapy before steroid therapy was initiated Up to 200 mg cortisone was given daily and withdrawal was started by slowly decreasing the dose as soon as the patient was able to sit in a wheel chair Sputum remained positive during the period of observation All 3 patients showed a favorable response to antituberculosis chemotherapy after steroid therapy had been started

Much of the fear of the use of steroids in the presence of active tuberculosis was based on animal experiments performed under conditions not comparable to clinical situations Bad clinical experiences were mostly attributable to resistance to antituberculosis drugs or to administration of steroids without antibiotic coverage These 3 cases support the mounting evidence in the literature that advanced ac

(1) A I t M d. 46 332 341 F bru ry 1957

tive pulmonary tuberculosis especially in debilitated persons responds well to therapy which combines steroid hormones with antituberculous therapy provided the antibiotic dosage is adequate and drug resistance does not develop Whether the tuberculous process itself can be influenced or whether the effect is due to symptomatic improvement is undecided

Cycloserine Combined with Other Antituberculous Agents in Treatment of Pulmonary Tuberculosis Cycloserine derived from Streptomyces orchidaceous has useful antituberculous properties which have been proved in man Israel G Epstein K G S Nair and Linn J Boyd (New York) gave cycloserine and isoniazid to 43 previously untreated patients with moderately to far advanced pulmonary tuberculosis

Cycloserine in full daily doses of 1 Gm plus 300 mg isoniazid daily or 1 Gm *streptomycin twice weekly* resulted in no additive toxicity The combination of cycloserine and isoniazid resulted in prompt and marked antituberculous activity—clinical improvement weight gain roentgenographic clearing and reversal of infectiousness The dose could be reduced to 0 5 Gm cycloserine daily and 4 mg /kg isoniazid without altering the therapeutic effect and the incidence of side reactions was reduced

Cycloserine in doses of 1 Gm /day combined with streptomycin 1 Gm twice a week gave results only slightly less prompt and marked than did the isoniazid cycloserine combinations The results were similar to those from the usual isoniazid PAS regimen

Clinical resistance to isoniazid cycloserine therapy has not *developed Sputum conversion has been so rapid* that tests for resistant bacilli were precluded in most cases after 24 weeks of therapy

Side effects have been almost exclusively neurologic tremors and hyperreflexia clonic convulsions and psychotic changes When the daily dose of cycloserine was reduced to 0 5 Gm only 1 patient showed any side effects and he had a single nocturnal clonic convulsive movement

Smaller doses of cycloserine than heretofore used combined with isoniazid constitute a nontoxic highly effective

(2) Am R v T berc. 75 553 575 Ap ll 1957

regimen for the treatment of pulmonary tuberculosis This combination is superior to other therapy in speed and degree of clinical response

► [The most encouraging feature of the studies on cycloserine by Epstein and his colleagues is the considerable success observed in the series treated with isoniazid and cycloserine in which the cycloserine dosage is held sufficiently low (250 mg twice daily) so that the incidence of neurotoxic reactions is materially reduced In a later progress report concerning this same series there was still only the single questionable reaction here mentioned. The therapeutic efficacy of the regimen appears to be of a high order—if not actually superior to isoniazid *PAS* or isoniazid *streptomycin* at least in the same class If the experience hold in longer series with respect to the very low toxicity this may well prove to be the most advantageous regimen of any for initial therapy Or possibly a modification with concurrent pyridoxine administration may permit higher doses of both isoniazid and cycloserine —Ed]

Role of Pyrazinamide in Chemotherapy of Chronic Pulmonary Tuberculosis Clinical Evaluation of 39 Cases Treated with Rotation Therapy is reported by Arthur A Calix and Kathleen White[3] (Decatur) Pyrazinamide and isoniazid combined have been demonstrated to be the most potent antituberculosis drugs but because of toxicity the former has not been used in cases which may be amenable to conventional chemotherapy and has not been used alone because the tubercle bacilli rapidly develop resistance

The 39 patients treated were selected because they had continued to expectorate tubercle bacilli despite extensive chemotherapy All but 3 had received long courses of isoniazid all had received streptomycin and most had received PAS Five had previously received pyrazinamide 22 had received viomycin

The course of therapy was pyrazinamide 3 Gm daily in divided doses plus isoniazid 4 mg /kg both continued for 2 weeks then viomycin 2 Gm daily was substituted for the isoniazid for another 2 weeks and for the next 2 weeks the combination of viomycin and isoniazid was given This course of 6-week rotation was repeated

The sputum was converted to negative by concentrate and culture in 13 of the 39 patients and 3 others have become negative by smear but not by culture Ten of these reported symptomatic improvement as did 8 whose sputum did not become negative

Toxic effects were anorexia nausea vomiting malaise

(3) J M A Al bam 6 81 86 O t be 1956

myalgia and arthralgia Jaundice and severe hepatic insuf ficiency occurred in 1 patient Five patients died but only 1 (the patient in whom liver toxicity developed) was consid ered to have died as a result of the drug

The study demonstrated that pyrazinamide can be effec tive in patients who have received pyrazinamide or isoni azid in the past by the use of a rotational chemotherapy schedule Pyrazinamide should be reserved for seriously ill patients who have not responded to the usual chemotherapy

Isoniazid Alone in Treatment of Pulmonary Tuberculosis Two Years Experience in Previously Untreated Patients Federico Vargas Jimenez[4] (Lima Peru) reports on 43 pa tients with advanced pulmonary tuberculosis treated for the

RESULTS IN PATIENTS WITH PULMONARY TUBERCULOSIS TREATED WITH ISONIAZID*

Months Afte Start f Th rapy	6	12	18	2
) All Cases				
N mbe of cases observed	43	40	36	34
S bst t l oe tge og ph mp o eme t	26 (60)	30 (?0)	34 (94)	32 (95)
Bacter l g c co ersion	27 (63)	31 (77)	26 (??)	28 (83)
C t es closed	8 (21)	19 (51)	20 (60)	22 (71)
Roe tg g ph c deteriorat n	3 (7)	1	4	3 (9)
Bacteri l g c rel pse	0	1	4	2 (6)
b) Mod t ly Ad ced				
N mbe of cases observed	17	15	15	15
S bst nt al roe tge g ph c mpro m t	15 (68)	14 (93)	15 (100)	15 (100)
B ct riolog c c vers	14 (82)	13 (87)	12 (80)	13 (??)
C t closed	5 (38)	10 (83)	11 (9)	11 (9?)
Roentge g ph d t t o	0	0	1	0
B teriol g c lap e	0	0	1	0
) F Ad n ed				
Number f a es ob rv d	26	25	21	19
S b t t l roe tg gr ph c imp o eme t	11 (42)	16 (64)	19 (91)	17 (90)
B t ri l g c rs o	13 (50)	18 (72)	14 (5)	15 (?9)
Ca ties losed	3 (12)	9 (42)	9 (40)	11 (61)
Roentg g phic d t ri t	3 (12)	1	3	3 (16)
B te l g r l ps	0	1	3	2 (11)

*Dosage 5 10 mg /kg /day Percentage di tribution in parenthes s

first time for 9 21 months with oral isoniazid 5 10 mg /kg daily Follow up for 2 years on 34 showed 32 with substan tial x ray improvement (table) Seven patients had relapse

(4) Am. Rev Tuberc 74 903 916 December 1956.

6 after isoniazid had been stopped 6-12 months There were 19 instances of extrapulmonary tuberculous complications in 14 patients before therapy was begun All responded satisfactorily to isoniazid alone These results compare fa vorably with those for combined therapy The rate of cavity closure at 12 months was similar to that with combined therapy

There were no signs of isoniazid resistance during the time the drug was given Unfavorable x ray changes and bacteriologic relapse were reversed or restrained when iso niazid was readministered suggesting that these relapses were benign Side reactions to isoniazid occurred in only 1 case

CASE 2—Man 29 had far advanced pulmonary tuberculosis (Fig 48 *A* and *B*) with hemoptysis for 3 years Two sinuses



Fg 48—X f p t ent w th f ad ced pulmon ry t ber l (Court y f J men F V Am R Tuber 74 903 916 Decembe 1956)

drained from the neck He received isoniazid 5 mg/kg/day Gas tric cultures became negative in 6 months He discontinued the drug against advice in the ninth month Seven months later he returned with hemoptysis and tubercle bacilli in the sputum shortly after a chest trauma (*C*) Gastric cultures again became negative 2 months after another similar course of isoniazid.

CASE 4—Boy 16 had pneumonic cavitary tuberculosis of the left upper lobe (Fig 49 *A*) which had been active for 10 months He also had enlarged lymph nodes in the neck axillae and abdo men left pleurisy with effusion and peritonitis with ascites He re ceived isoniazid 10 mg/kg/day for 12 months Treatment was discontinued for 3 months and then resumed for the rest of the ob servation period The pleurisy cleared promptly (*B*) Gastric cul tures became negative and the cavity closed during the 17th month of observation X rays (*C* and *D*) made about 2 years after treat

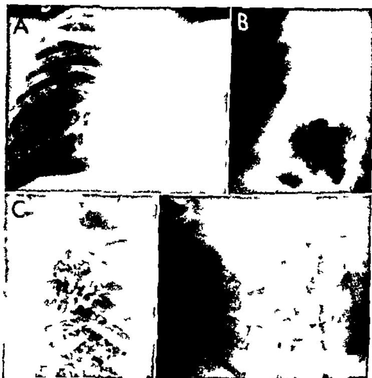


Fig 49 —X ys of pat t w th pne mo c ca ta y t be c lo of left pp l be (C rt y of J me F V Am. Rev Tuberc 74 903 916 Decembe 1956)

ment was started showed bronchiectasis persisting in the apicoposterior segment and calcified lymph nodes in the neck and abdomen

► [This interesting report confirms our conclusion of several years ago (Deuschle *et al* Am Rev Tuberc 70 228 1954) that isoniazid alone is comparable with the more commonly used 2-drug regimens It also goes further by showing significant benefit from continued therapy in the second year after failure of cavity closure and sputum conversion in the first year The importance is not so much relative to reopening the question of what patients can or should receive single drug therapy as in the light this experience sheds on the long term efficacy of isoniazid and the question of its optimal dosage Other drugs will probably become available (see Epstein *et al* this YEAR BOOK p 188) as companions to isoniazid which *may substitute for streptomycin or PAS leaving this pair in re*serve as a unit The trend toward postponing surgery to as late a date as possible makes it even more desirable to keep streptomycin PAS in reserve for pre and postoperative coverage If less toxic and less inconvenient regimens than isoniazid streptomycin or isoniazid PAS can be used in initial therapy it will be also an advantage One such regimen which has been long available although it is still shunned by many clini

cians is isoniazid alone. For selected cases it may be the optimal regimen for initial treatment especially in situations where this must be undertaken outside a hospital —Ed.]

Giant Air Cysts as Sequela of Pulmonary Tuberculosis Six cases are presented by John L. Shek Jerome A Cope and Gordon D Myers [5] All had pulmonary tuberculosis and had been treated for varying periods The air cysts in the lung fields seen by x ray could all be traced from areas of tuberculous infiltration and were the outcome of continuous resolution and regression of the tuberculous process In the x rays they appeared to be giant bullae of the lung or pneumatoceles Examination of the resected specimens gave no histopathologic evidence of tuberculosis

Acquired air cysts of the lung develop when surrounding tissue contracts interalveolar septa break down and the bulla coalesces and distends This mode of formation seems applicable to air cysts which develop after pulmonary tuberculosis

Serum Proteins in Pulmonary Tuberculosis Albumin concentration is decreased and globulin increased in many diseases Most observed changes are not diagnostic of a par

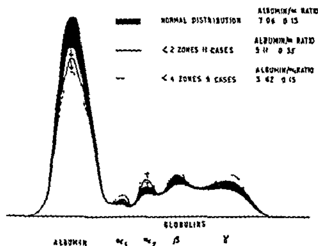


Fig 50 —Serum prot pulmonary tuberculosis. (Courtesy E G Illand I C., I Brit M J 1 1460 1464 Jun 23 1956)

(5) J Thorac Surg 32 96-10 July 1956

ticular disease but indicate its clinical severity These changes occur in tuberculosis

I C Gilliland R N Johnston Peter Stradling and E M Abdel Wahab[6] (London) studied serum protein fractions in 327 patients with pulmonary tuberculosis and 28 unaffected contacts used as controls Paper electrophoresis was done on all and consistent changes were observed (Fig 50) The albumin concentration fell and alpha globulin rose progressively with increasing activity and extent of disease Conversely these fractions were restored toward normal as the disease became quiescent and was arrested Treatment with antituberculosis drugs had a similar effect As an index of activity in tuberculosis the albumin alpha globulin ratio was much more sensitive than the sedimentation rate

Insensitivity to Tuberculin in Pulmonary Tuberculosis Based on statistics the value of the tuberculin test cannot be disputed but nearly all authors who have studied large series have reported exceptions to the general rule that patients with active tuberculosis react to tuberculin Since 1951 J G Scadding[7] (London) has given intradermal tuberculin tests with 1 10 and 100 tuberculin units (T U) of PPD to patients with pulmonary tuberculosis Of 107 patients tested 4 have persistently failed to react to 100 T U although tubercle bacilli were found in their sputum and the clinical and x ray diagnosis was chronic indolent pulmonary tuberculosis

Rich stated A genuinely and persistently negative test is strong evidence against the presence of active tuberculosis except in practically moribund patients intercurrent infections cachectic states late pregnancy and the puerperium and hypothyroidism To this list must be added the cases of indolent pulmonary tuberculosis Patients with this disease are usually considered to have sarcoidosis because of the clinical course and negative reaction to tuberculin skin tests The distinction between sarcoidosis and indolent pulmonary tuberculosis with low tuberculin sensitivity is indefinite At least some of the cases which may properly be called sarcoidosis may be a manifestation of infection with the tubercle bacillus

(6) Brit. M J 1 1460 1464 J e 23 1956
(7) T bercle 37 371 380 1956

Consideration of Chronic Pulmonary Parenchymal Inflammation and Alveolar Cell Carcinoma with Regard to Possible Etiologic Relationship Alveolar cell tumors are primary pulmonary neoplasms arising in the peripheral portions of the lung and characterized by cuboid or tall col



Fig 51 —Aden matous p th lial hyperpla ia n ea of ch on inflammation. Usual 1 w boidal epith lium (rrow) in ea f hronic infl mmation d fibros long w th tall l m ll h cteristi f l l ll carcinoma. (Courtesy f Bea D L. d Sh p J L Am. J Med. 21 879 887 Decembe 1956)

umnar epithelial cells lining alveolar septa with no associated desmoplasia The diagnosis is absolute only if no intrinsic bronchial tumor or primary adenocarcinoma is found elsewhere Pulmonary adenomatosis and alveolar cell carcinoma are probably variants of the same tumor representing different degrees of malignancy

David L Beaver and John L Shapiro[8] (Vanderbilt Univ) present 7 cases of typical alveolar cell carcinoma and 1 ex

(8) Am J Med 21 879 887 Decemb 1956

hibiting the microscopic changes associated with this condition apparently on the basis of metaplasia of epithelium subsequent to chronic inflammatory disease In this case early changes indicative of the lesion were present (Fig 51) and offered evidence of the relationship between chronic pneumonitis and alveolar cell carcinoma

Alveolar cell carcinomas may arise in or are associated with inflammatory foci in the lung They probably arise in a single focus and metastasize first throughout the ipsilateral and then the contralateral lung via mucous sections or aerially Alveolar epithelial metaplasia may represent a precancerous phase of cellular growth

The increasing incidence of alveolar cell carcinoma parallels and may be related to the reported increased incidence in pulmonary fibrosis

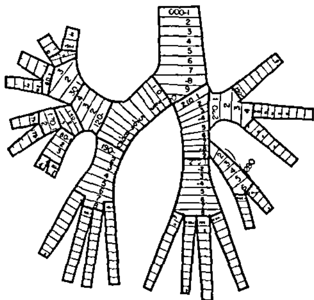
Changes in Bronchial Epithelium in Relation to Smoking and Cancer of Lung Report of Progress *Oscar Auerbach J Brewster Gere Jerome B Forman Thomas G Petrick Harold J Smolin Gerald E Muehsam Digran Y Kassouny and Arthur Purdy Stout*[9] (VA Hosp East Orange N J) studied 150 white men aged 22 88 of diverse occupational backgrounds who died and came to autopsy Data on occupations residence and smoking habits were obtained from the family by a trained social worker or whenever possible from the patient on hospitalization The material was studied only after smoking histories had been obtained All patients dying of lung cancer were included The tracheobronchial tree was dissected from the lungs as soon as possible fixed and divided into 208 portions (Fig 52) Sections were studied by microscope without knowledge of smoking histories

Definite carcinoma in situ was found in 6 3% of the slides from the 34 patients with lung cancer and borderline findings were present in another 6 7% of the slides These changes were noted in 28 of the 34 patients The 83 who died without gross evidence of lung cancer were divided into three groups according to smoking history Among the 16 who never smoked regularly 18 6% of the slides showed basal cell hyperplasia compared with 36 1% in the 47 who smoked over a pack a day a statistically significant difference Among the group who never smoked regularly only

(9) New England J Med 256 97 104 Jan 17 1957

29% of the slides showed 5 or more rows of basal cell hyper plasia compared with 10 8% in those who smoked over a pack a day Among these two groups stratification was found in the slides in 4.2 and 10 4% squamous metaplasia in 1 9 and 9 5% carcinoma in situ in 1 and 6% respectively

It has previously been shown that increased rate of bron chogenic carcinoma is associated with certain industries such as ore mining chromate production nickel refining asbestos manufacturing and gas work urban compared with



F g 52 —T heobr hial t how g d tribut on f 208 sect on (Courtesy f A ba h O t l New E gland J M d. 256 97 104 J n. 17 1957)

rural areas and inflammatory processes Also constitu tional factors as yet unknown are important

This histologic study showed that among persons who died of causes other than lung cancer basal cell hyperplasia stratification squamous metaplasia and carcinoma in situ were least frequent in those who never smoked regularly with a progressive increase in moderate and heavy smokers The same but more extensive changes were observed in

hibiting the microscopic changes associated with this condition apparently on the basis of metaplasia of epithelium subsequent to chronic inflammatory disease In this case early changes indicative of the lesion were present (Fig 51) and offered evidence of the relationship between chronic pneumonitis and alveolar cell carcinoma

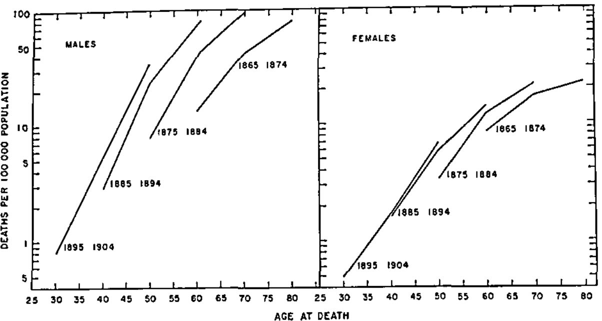
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Changes in Bronchial Epithelium in Relation to Smoking and Cancer of Lung Report of Progress Oscar Auerbach J Brewster Gere Jerome B Forman Thomas G Petrick Harold J Smolin Gerald E Muehsam Digran Y Kassouny and Arthur Purdy Stout[9] (VA Hosp East Orange N J) studied 150 white men aged 22 88 of diverse occupational backgrounds who died and came to autopsy Data on occupations residence and smoking habits were obtained from the family by a trained social worker or whenever possible from the patient on hospitalization The material was studied only after smoking histories had been obtained All patients dying of lung cancer were included The tracheobronchial tree was dissected from the lungs as soon as possible fixed and divided into 208 portions (Fig 52) Sections were studied by microscope without knowledge of smoking histories

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(9) New England J Med 256 97 104 Jan 17 1957



F g 53 —D th t f m ca er f l g b h d pleu a p 100 000 pop l t on between 1930 nd 1950 f ohorts born n suc decad (C t y f Hae el W nd Sh mk M B J Nat. C e I t. 16 1417 1441 J n 1956)

those who died of carcinoma of the lung Although definite carcinoma in situ was present in all groups with a parallel rise in proportion to increasing cigaret consumption there was an almost similar distribution of this change in those who smoked over a pack a day (6%) and in the cases of bronchogenic carcinoma (6 3%) These findings are consistent with the hypothesis that inhalants are important in causing bronchogenic carcinoma and that cigaret smoking is an important factor

► [The large number of cases with multiple lesions diagnosed carcinoma *in situ is surprising since few instances are encountered clinically in which* multiple origin of lung carcinomas seems probable except in the so called alveolar or bronchiolar carcinoma which is not here under consideration. —Ed]

Smoking Patterns and Epidemiology of Lung Cancer in United States Are They Compatible? Retrospective studies on patients with pulmonary cancer and forward studies in which smoking histories were collected first and persons followed to determine subsequent lung cancer mortality uniformly reveal an association between smoking and lung cancer *These studies have been criticized* because the groups were selected and because smoking constitutes a self selected group William Haenszel and Michael B Shimkin[1] (Nat'l Inst of Health) statistically investigated reported results compared with the distribution of lung cancer to find if they were valid for larger populations

Since lung cancer occurs among nonsmokers this risk can be expressed as a unit risk Retrospective and prospective studies on white males show differences of the order of 7 8 1 between cigaret smokers and nonsmokers and for smokers who consume over a pack daily the ratio may rise to 13 15 1 The consistency between retrospective and forward studies suggests that more of the former and extension of the follow up period in forward studies would not materially alter statements of relative risk already obtained

The relative risks can be listed as nonsmokers of cigarets 1 discontinued regular cigaret smokers 3 and regular cigaret smokers—½ pack or less 4 ½ 1 pack 8 and more than 1 pack daily 13 This model is applied to analysis of the sex urban rural and white nonwhite ratios and to regional variation and different time periods

(1) J N t Cancer In t. 16 1417 1441 J 1956

of lung cancer but the magnitude of the change is too great and comparable changes have not occurred for female lung cancer Few women were smoking cigarets regularly before 1930 The weak carcinogen present requires a latent period of at least 15 years so little effect on cohort relationships could have been expected before 1945 and the rise before 1935 attributed to other factors including increased recog nition

Observed ratios of lung cancer rates and ratios predicted agree reasonably closely (Fig 54) The two major devia tions from a straight line occur in the sex ratio and male urban rural ratio Evidence favors conclusion that the ex cess lung cancer risk among cigaret smokers seen in special study groups occurs also in the total population

► [The authors take up some of the criticisms by Berkson (see 1956-57 YEAR BOOK p 143) in which doubt was cast on the validity of the sam pling methods in such prominent studies as those of Doll and Hill and of Hammond and Horn. They conclude that the findings in the special studies relative to an association between cancer and smoking are probably valid for the total population and that they are compatible with other informa tion on the distribution of lung cancer

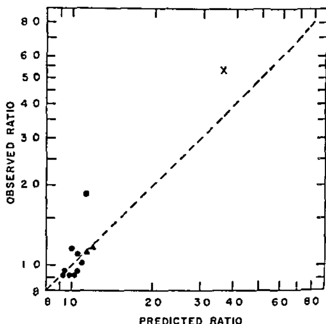
This is not likely to settle the controversy nor will the following two papers (by Doll and Hill and by Wynder *et al*) even if these add more statistical evidence to the well documented association. As matters stand the question remains open or so it seems to me whether the statistical association is causally as significant as it appears Some of the studies prove too much," as was suggested by Berkson raising the question What disease does cigaret smoking not cause? In this sense the *Second Report on Mortality of British Doctors* (Doll and Hill following ab stract) is at variance with the American Cancer Society studies of Ham mond and Horn since it reveals no statistically significant trend with respect to such causes of death as peptic ulcer and pulmonary tuberculosis and only a slight relationship between smoking and coronary thrombosis —Ed]

Lung Cancer and other Causes of Death in Relation to Smoking Second Report on Mortality of British Doctors is presented by Richard Doll and A Bradford Hill[2] Over 40 000 men and women in the British Medical Register re plied to questionnaires about smoking habits They were then classed as nonsmokers and smokers of 3 different amounts by cigaret pipe or both Mortality of each group has been recorded for the ensuing 4½ years The study re lates to men over age 35 of whom 1 714 died including 81 from lung cancer

Death rate from lung cancer increased steadily and mark

(2) Brit M J 2 1071 1081 Nov 10 1956

The modified sex ratio predicted for all ages over 35 is 3 6 1 The observed 5 1 ratio implies a male excess in lung cancer mortality of about two fifths which cannot be explained by standardization for smoking history Smoking histories account for only part of the urban rural differences and the risk for male nonsmokers and smokers in



F g 54—Summary of bserv d a d p edi t d rat f l ng ca t d v d f om c mp g p pulat on gro ps for ex (X) u ban ru al re den (ol d squ r) l (sol d t a gl) and eg on (lid c le) (Courte y of Haen l W a d Sh ik M B J Nat. Can r Inst 16 1417 1441 June 1956)

urban environments is apparently greater Differences in relative risks between white and nonwhite populations are small and can be attributed to differences in smoking habits

Groups of persons (cohorts) born during successive decades experience greater lung cancer mortality at comparable ages than their immediate predecessors (Fig 53) This is more prominent for lung cancer than for cancer of other sites and especially in men Such an effect could be produced solely by progressively improved recognition and diagnosis

► [The authors advance an ingenious explanation of why 40% of the cases of epidermoid carcinoma in women occurred in nonsmokers whereas the percentage of nonsmokers in men with lung cancer is only 1 % By constructing a hypothetical community in which 80% of women and 20% of males are nonsmokers and in which the lung cancer morbidity is 5/100 000 in nonsmokers and 30/100 000 in smokers the proportion of nonsmokers among the women with lung cancer works out to 40% This hypothetical construction postulates the premise that smoking "is a fundamental factor in the development of lung cancer whereas sex is not a factor at all." Calculations relating reported smoking habits in the general population to the sex ratio in the over all incidence of lung cancer are cited as indirect evidence in favor of this hypothesis since the calculations lead approximately to the observed ratio. Thus an apparent inconsistency is resolved, and the authors are satisfied that their data show that cigaret smoking increases the risk of epidermoid lung cancer in women as it does in men.—Ed.]

Radiotherapy of Cancer of the Lung Results in Selected Group of Cases In 1942 a patient with inoperable undifferentiated carcinoma of the bronchus was treated by x irradiation Gross x ray fibrosis of the right lung developed but the patient was alive well and working 13 years later Two other similar patients were treated with massive x rays and have survived more than 5 years Because of these results Joseph Smart and Gwen Hilton[4] (Univ College Hosp London) treated 33 selected patients by radiotherapy alone

Each patient was in good general condition the lesion was localized and so situated that surgery could be undertaken and there was no evidence of mediastinal gland involvement Proof was obtained by biopsy or positive sputum before treatment was begun Of the 33 cases 19 were squamous cell carcinoma and 6 anaplastic carcinoma A dose of 5 000-5 500 r was delivered to the tumor if it was a squamous cell carcinoma but only 4 000-4 500 r if undifferentiated Daily dose was decreased or treatment suspended for a day or two if temperature rose or pulse and respirations increased

Of the 33 patients 12 have been followed for 5 years or more Four (3 with squamous cell and 1 with anaplastic carcinoma) are still alive and well One patient survived 3 years 2 survived 2 years or more and 5 died within the first 2 years In this limited number of cases the survival rate was 33% a figure similar to surgical results

In a previous report 4 patients treated by x rays alone had no macroscopic evidence of the original growth at au

(4) Lancet 1 880 881 J 19 1956

edly with the amount smoked Death rate/year rose from 0 07/1 000 in nonsmokers to 0 47 in light 0 86 in me dium and 1 66/1 000 in heavy smokers Mortality from lung cancer was significantly greater in cigaret smokers compared to pipe smokers

There was little difference between the smoking habits of doctors resident in Greater London in large towns or in other districts Contrasts in lung cancer mortality be tween smokers and nonsmokers therefore cannot be attrib uted to differential exposure to atmospheric pollution Mor tality from coronary thrombosis apparently showed a sig nificant relation with smoking but this was distinct only at ages 25 54 years Three other causes of death chronic bron chitis peptic ulcer and pulmonary tuberculosis showed steady increase in mortality from nonsmokers to heavy smokers but only in chronic bronchitis was it statistically significant

Lung Cancer in Women Study of Environmental Factors Ernest L Wynder Irwin J Bross Jerome Cornfield and Walter E O Donnell[3] obtained information on smoking occupation and residence from 196 women with proved can cer of the lung and 1 304 women who had cancer or benign tumors at other sites

In women with epidermoid lung cancer a larger proportion smoke cigarets and more heavily (a pack or more a day) than in groups with adenocarcinoma of the lung or tumors at other sites In the control group as in the sample of the United States female population smoking habits of women change with age about half the women under 50 and most over 50 are nonsmokers and less than 2% of women over 50 smoke as much as a pack a day About 4% below age 50 smoke one or more packs a day

Smoking habits of women in the control group are minimal compared to those in a control group of men Most men over 40 use tobacco and a large majority of women in this age group do not most men over 40 who smoke cigarets consume at least a pack a day whereas few women over 40 smoke this much Even in age groups under 40 women with tumors at other sites the control group have minimal smoking habits in relation to male controls

(3) N w Engla d J Med. 255 1112 1121 Dec. 13 1956

gery to be inoperable This mistake may have occurred in the 33 cases reported with x irradiation alone

A more detailed analysis of the results is shown in Tables 1 and 2 The survival rate is calculated by the life table method In the series treated by radiotherapy the 2 year survival rate is 55 6% compared to 45% for cases treated by surgery At least 10% of patients treated surgically died within 2 months of operation and were excluded from the series further reducing the 2 year survival rate for surgery The probability of such a large difference being due to chance alone is between 0 1 and 0 2

MISCELLANEOUS

Clinical and Pathologic Study of Endometriosis of Lung The term vicarious menstruation refers to recurring hemorrhages from nasal or tracheobronchial passages in women with a chronology which suggests correlation with the menstrual cycle These have been ascribed to extragenital endometriosis but documented cases of pulmonary endometriosis have not been reported Such a case is reported by R Lattes F Shepard H Tovell and R Wylie[5] (Columbia Univ)

Woman 34 for 3 years had hemoptyses associated with menses They began after a cesarean section and endometrial curettage for menorrhagia and continued irregularly despite various hormone treatments until she again became pregnant. At this time a chest x ray previously negative showed a discrete coin lesion in the right middle lobe Exploratory thoracotomy followed by segmental resection showed the mass to be endometrium with marked decidual reaction of the stroma (Fig 55) It was this decidual reaction which caused the previously present and functioning endometrial implant to enlarge and become detectable by x ray The patient was delivered at term by cesarean section and has had no further hemoptyses

The theory of hematogenous metastasis best explains the sequence since the first hemoptysis followed two surgical procedures on the uterus A fragment of viable endometrium probably entered a uterine vein and was transported to the lung where it responded to stimulation of the ovarian hormones Small emboli probably reach the lung frequently during delivery or surgical procedures on the pregnant

(5) S g Gynec. & Obst. 103 55 558 Novembe 1956

TABLE 1—SURVIVAL RATES OF PATIENTS AT TWO-MONTH INTERVALS AFTER RADIOTHERAPY

INTERVAL (COMPLETED MO FROM BRONCHOSCOPY)	AT RISK AT START OF INTERVAL	SURVIVAL RATE %
0 2	33	100 00
3 5	32	100 00
6 8	30	96 83
9 11	29	96 83
12 14	23	76 80
15 17	22	73 46
18 20	20	70 04
21 23	18	63 04
24-26	14	55 63
27 29	10	43.27
30 32	7	38 46
33 35	7	38 46
36 38	6	38 46
39-41	5	32 05
42 44	5	32 05
45 47	5	32 05
48 62	4	32 05

TABLE 2—SURVIVAL RATES OF PATIENTS LIVING LONGER THAN TWO MONTHS AFTER OPERATION*

INTERVAL (COMPLET MO FROM OPERATION)	AT RISK AT START OF INT R AL	SURVIVAL RATE %
0 2	453	94
3 5	423	82
6 8	367	73
9 11	326	63
12 14	282 5	58
15 17	259 5	54
18 20	237	51
21 23	222	47
24 26	204 5	45
27 29	188	43
30 32	174	41
33 35	162	39
36-47	133	35
48 59	85	33

*T ken f om Bignall d Moon (Th ax 10 183 1955)

topsy suggesting that in some cases it can be adequately treated by radiotherapy Three other factors which may influence the good results are (1) no immediate mortality after radiotherapy compared with an immediate postoperative mortality of about 10% (2) apparent decrease in cerebral metastases as compared to surgery and (3) the high incidence of cases originally considered operable proved at sur

lowed by implantation and growth of endometrial emboli

Chronic Localized Pulmonary Brucellosis Three cases are reported by Lyle A Weed Pierce T Sloss and O Theron Clagett[6] (Mayo Clinic and Found) All patients had well defined densities of the lung on x ray study Laboratory examination showed each lesion to be a caseous granuloma and Brucella suis was isolated in culture from each patient Mycobacterium tuberculosis fungi actinomyces and common pyogenic bacteria were excluded

The same dilemma in preoperative diagnosis was present as in coin lesion of the lung and isolated pulmonary nodule Bacteriologic examination of the sputum or bronchial washings skin tests and agglutinations tests have rarely been of help

The gross appearance of the granulomas was essentially the same in all 3 cases It mostly consisted of firm friable caseous material enclosed in a thin shell of fibrous connective tissue infiltrated by lymphocytes Between this and the necrotic central material was a layer of epithelioid cells in places showing palisade arrangement A few Langhans multinucleated giant cells were present Nothing histologically in these granulomas distinguished them from the usual caseous granulomas produced by M tuberculosis Coccidioides immitis or other infectious agents However by special methods brucella were isolated and identified

In reports of surgically removed localized granulomas of the lung the lesions are often called tuberculomas Some of these may be due to agents other than M tuberculosis As such material is subjected to future thorough laboratory investigation more reports of brucella as a cause of localized granuloma will appear

Idiopathic Pulmonary Hemosiderosis in Adult Only 15 cases in adults have been reported in the literature Another is presented by N Wynn Williams and R Douglas Young[7] Of the 16 cases 12 have been in men Diagnosis was most frequently made by clinical examination and x ray It was confirmed by biopsy in 2 and by autopsy in 5 In 6 patients there was no x ray evidence of abnormality at the first ex

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(6) J A M A 161 1044 1047 J ly 14 19 6
(7) Th x 11 101 104 1956

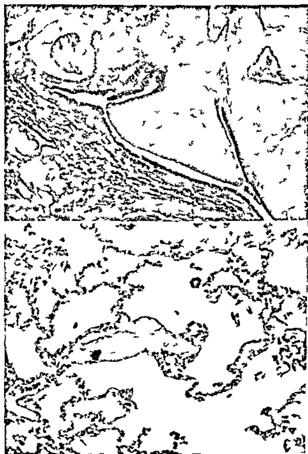


Fig 55 (top) —Low power ph t m ograph f l s on. Polypo d mass of dec du l t s e p ojects int lum n f b onchu nd in upper secto e 2 d lat d e domet ial gla d H m toxyl n eos n

F g 56 (bott m) —Small embol of decid al cell n lu g of w m wh died du ing del ery M y m la emboli we f und cap ll ries of i teral olar epta. Hem t xyl n-e n

(Courtesy f Lattes R *et l* Su g Gynec & Obst. 103 552 558 No emb r 1956)

uterus but apparently only exceptionally do these implants survive An autopsy of a woman who died during delivery revealed multiple clusters of decidual cells apparently em bolizing the capillaries of the interalveolar septa (Fig 56)

The most logical explanation of extraperitoneal endome triosis is that of a benign hematogenous metastasis fol

amination although symptoms were severe enough to bring the patient to his physician In 1 there was no radiologic abnormality at the time of death Prognosis is serious Two patients are reported alive after 4 years The rest are dead or have been followed only a short time (table)

Man, 26 complained of lassitude but no cough He had left sided pleurisy 5 years previously X ray showed a slightly enlarged left hilar shadow Six months later he had another episode of left sided pleurisy and x ray showed obliteration of the costophrenic angle. He was readmitted 18 months later for increasing lassitude, dyspnea on exertion and an episode of vomiting bright red blood. Anemia was treated by transfusions and iron. Six months later routine chest film revealed *fine nodular stippling over the lower half of each lung field* He had repeated small hemoptyses Hemosiderin laden phagocytes were found in sputum. A lung biopsy confirmed diagnosis of idiopathic pulmonary hemosiderosis The patient had another episode of anemia and stained sputum from which he recovered. X rays revealed increased nodulation

Varicella Pneumonitis Although chickenpox is regarded as the mildest of the exanthematous diseases of childhood it can produce serious illness and even death All five lobes



Fig 57 (Courtesy of E d Z. F d Schnell F R. *Radiology* 66 723 726 May 1956)

Certain Data on 16 Cases of Idiopathic Hemosiderosis Diagnosed over Age 14 Years

Author	Sex	Method of Diagnosis	Age at First Symptoms	Age at Diagnosis	Length of Follow up	Outcome	First Chest Radiograph Normal after Onset of Symptoms
W ld str m J (1940)	F	Radiology Necropsy	16	16	2 years 8 months	Death	No
B rson N ht ebel Ö (194)	M		Not stated	38	Nil		Not stated
Kerley P (1951) 1	M	Radiology		20–30	Not stated	Not stated	
2	M			20–30			
3	F			0			
4	M			19			
5	M	Biopsy		8	4 years	Alive	
W lton M and W ll ms A A (1951)	M	Radiology	16	17	2	Death	Yes
Ta t G B and Co da M (195)	M	Necropsy	31	?31	Nil		Yes All chest radiographs normal
Cliff J M (1953)	M	Radiology	0	0	2 years	Alive	No
M derso W C (1954)	M		Before 18	19	4		
Sandoe E (1954) 1	F		Childhood	19	6	Death	Yes
2	M		13	?15	1 year	Alive	
Hamer N A J (1955)	M		13	19	Few months		
Wagn r K (1955)	F		21	22	3 years	Death	
Wynn W ll ms N and Y g R D	M	Necropsy Radiology Biopsy	8	9	Few months	Alive	No

amination although symptoms were severe enough to bring the patient to his physician In 1 there was no radiologic abnormality at the time of death Prognosis is serious Two patients are reported alive after 4 years The rest are dead or have been followed only a short time (table)

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Fig 57 (Co rt y f E d Z F a d Sch ll, F R. Rad logy 66 723 726 M y 1956)

of the lung are rarely involved In a case reported by Z F Endress and F R Schnell[8] (Pontiac Mich) onset of pul monary involvement parallelism with skin changes normal white blood cell count and lack of definite response to anti biotics agreed with the findings in other reported cases Roentgenographically the condition produces a widely dis seminated nodular infiltration involving all five lobes (Fig 57) with onset early in the second week of illness

The lung infiltrates vary a little in size and shape They are produced by confluence of many small areas of consolidation around small foci of necrosis caused by the virus Initial clearing is rapid and partial Subsequent regression is slow sometimes requiring months Clinically severe dyspnea cya nosis and hemoptysis are commonly associated Nephritis encephalitis hepatitis pericarditis orchitis and laryngitis may accompany the pneumonia

Schistosomiatic Cor Pulmonale and Myocarditis Clin ico Pathologic Considerations in Two Cases are discussed by Oscar Monteiro de Barros Fortunato Gabriel Giannoni Carlos Marigo and Feliciano Jose Frizzo[9]

CASE 1—Youth 17 had a predominantly cardiac syndrome with gallop rhythm venous stasis and tachycardia Its clinical and ECG resemblance to Chagas disease in its terminal phase was explained at autopsy by generalized myocarditis with eosinophilic exudate caused by schistosomiasis Several adult specimens male and fe male of Schistosoma mansoni were found in the mesenteric vessels The cerebellum corpus striatum and occipital lobe showed lesions caused by parasite eggs The leptomeningeal vessels also contained parasites In the lungs there were diffuse serous arteritis and focal arteritis of the walls caused by passage of the eggs i e granulomas with eggs in the parenchyma and arteriovenous fistulas

CASE 2—Youth 20 had vertigo and fatigue for 6 months and he moptysis for 1 month The clinical picture was that of cor pulmo nale with fine rales in both lung bases cardiac dilatation and hypertrophy and stasis of the pulmonary circulation The liver was enlarged Cyanosis and edema were absent The eggs of *S man soni* were found in the feces but rectal biopsy was negative There was marked eosinophilia (23%) without anemia Fever and bloody sputum persisted for 35 days then after preparation with antibi otics a pulmonary biopsy was done Complications developed 5 days later which led to collapse and death within 18 hours

Histologic study of sections obtained at autopsy showed numerous adult S mansoni of both sexes in the mesenteric vessels The lungs

(8) Rad ology 66 723 726 M y 1956
(9) Arq Hosp S t C sa Sã Pa lo 2 1-40 Ma ch 1956

and liver were invaded by eggs which were seen also occasionally in the myocardium There were numerous granulomas and eggs in the central nervous system The pulmonary lesions consisted of re action granulomas to eggs and intense serous arteritis (edema and proliferation of intima) or true arteritis (inflammatory infiltration in wall) which reduced the lumens granulomas were generally lo calized at the side of the vessels with involvement of the wall itself by passage of the eggs through arteriovenous fistulas The liver showed intense connective tissue proliferation and fibrosis of portal



F g 58—W ll f t y (*A*) h p ng lent d tow d v (*V*) u t d by p ll y l fib d nec (*F*) p b bly u d by gg m g f m t y t d c d f om ×85 (Court y f d B s O M *t l* A q H p S ta C a S P ul 2 1 40 M b 1956)

spaces involving vessels and biliary ducts besides partially necrosed eggs accompanied by a histiocytic reaction

The generalized schistosomiasis in these cases manifested by multiple localizations of the worm and its eggs in various organs demonstrates the potential gravity of this parasito sis Pulmonary localization of S mansoni has been observed by numerous authors Cerebral localization has not been re corded before in Brazil despite the numerous cases studied there The present cases demonstrated abundant adult para sites and eggs in the central nervous system and in the myocardium Dissemination of adult worms through the organism probably is effected through arteriovenous fistulas

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(8) Rad ology 66 723 726 M y 1956
(9) Arq Hosp Sa t Casa S Pa lo 2 1-40 M h 1956

trypsin which has been reported to induce metaplasia None of the 65 patients who had inhalations before bronchoscopy had any reaction Of 28 who had proved carcinomas 16 (57%) had positive cytologic studies and 4 (14%) doubtful There were no false positive results

Patients with acute pulmonary disease such as atelectasis secondary to mucus plugs or thick tenacious sputum re sponded rapidly and satisfactorily to pancreatic dornase Those with more chronic disease responded slower but re markably well while those with chronic pulmonary disease or malignancy responded poorly

Even with repeated inhalations and courses of inhalations few had minor complications Pancreatic dornase seems par ticularly useful in postoperative thoracic surgical and post traumatic patients with thoracic injuries

Tietze s Syndrome is a painful nonsuppurative swelling of the costochondral or sternoclavicular junction and should always be considered in differential diagnosis of chest pain Tenderness over the involved cartilage at times is extreme and may be exaggerated by effort as a result of increased thoracic movement Etiology is unknown No specific find ings are seen on x ray but radiologic and laboratory tests are helpful in excluding other causes of chest pain Treat ment consists of local applications of heat procaine infiltra tions salicylates and reassurance Two cases are reported by Michael Bernreiter[2] (Kansas City Mo)

CASE 1—Man 45 had pain over the left side of the chest in creased by coughing and exertion. He had a small tender swelling 3×3 cm at the third left costochondral junction Procaine infil tration gave immediate relief Six weeks later the mass was still present but tenderness was less pronounced Reassurance that the condition was benign and not of cardiac origin relieved the patient s anxiety

CASE 2—Woman 50 had severe pain in the upper left chest, made worse by moving A small tender swelling over the left sec ond costochondral junction was found and pressure induced severe pain extending to the left shoulder and arm Reassurance and local application of heat gave considerable relief Three months later the tender area was still present but distress was less pronounced

(2) Ann. I t. Med. 45 132 134 July 1956

eggs may also be deposited in situ since fecund females were found in various organs Cor pulmonale may be *caused by generalized pulmonary arteritis pulmonary fibrosis* and true arteriovenous fistulas containing eggs which must be important in causing pulmonary hypertension

In these cases extrusion of eggs through the vascular wall as the result of endothelial activity confirmed the findings of Koppisch Pulmonary arteriovenous fistulas are important in explaining the distribution of eggs to all organs through the general arterial circulation (Fig 58 Case 2) The finding of worms and eggs in the brain and heart suggests that at the time of infestation larvae transported to the pulmonary barrier became localized in these organs and developed into adults but the fact that both male and female specimens were found in all organs suggests fecundation and localization in the organs outside the usual natural habitat The immunobiologic reaction of the infested organism was shown in severe pulmonary vascular damage in all sections examined with reduction or disappearance of the arteriolar lumen owing to edema and intimal proliferation due to the allergic reaction to the antigen produced by the parasites and eggs

Pancreatic Dornase Aerosol in Pulmonary Endotracheal and Endobronchial Disease Atelectasis pneumonitis lung abscess and thick tenacious sputum are frequently important *in the morbidity and mortality of diseases Antibiotics* have controlled many infections but the obstructive phenomena remain unsolved Expectorants and vapor inhalations are limited in usefulness endotracheal aspirations or bronchoscopy are traumatic and not always successful Streptokinase streptodornase (Varidase®) trypsin and detergents such as Alevaire® have recently been introduced Eugene E Cliffton[1] (Mem l Center for Cancer New York) gave pancreatic desoxyribose nuclease (dornase) 100 000 units in 2 cc sterile diluent inhaled by nebulizer to 104 patients In 65 it was given before bronchoscopy and in 39 as treatment for pulmonary disease

Studies *of the bronchial tree by bronchoscopy failed* to show any significant change in 56 patients Biopsies and cellular cytology revealed no change contrary to the effect of

(1) D Chest 30 373 384 O t ber 1956

THE BLOOD *and* BLOOD-FORMING ORGANS

WILLIAM B CASTLE MD

PART III

THE BLOOD AND BLOOD FORMING ORGANS

GENERAL TOPICS AND BASIC CONSIDERATIONS

Bone Marrow in Ischemia Review of the literature indicates that the stimulating effect of anoxia on erythropoiesis is not produced by direct action on the bone marrow However there is evidence that anoxia can act on the bone marrow through a hormone intermediary Experiments have been performed in which blood or urine has been obtained from animals rendered anemic or subjected to anoxia Preparations of these have been injected into test animals and erythropoietic responses obtained Similar claims have been made in relation to man

In 2 patients with patent ductus arteriosus with reversed flow and anoxia of only the lower half of the body Stohlman and Schmid and Gilbertsen respectively found polycythemia and relatively increased erythropoiesis in the sternal marrow despite its normal oxygen saturation This is further evidence for a humoral intermediary

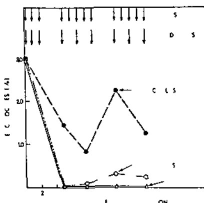
David A Sugerman[1] (Sydney) observed 11 ischemic lower limbs with clear clinical evidence of pronounced arterial disease In several arterial disease was proved by dissection and arteriography The bone marrow of the lower end of the femur and of the tibia was examined in these limbs and showed no macroscopic or microscopic evidence of erythropoiesis A similar lack was found in 2 normal controls in consonance with statements in the literature On the assumption that the bone marrow concerned had some degree of ischemia no morphologic evidence was found that ischemia directly stimulated erythropoiesis

[The only objection to this interpretation derives from the fact that

(1) M J A t 1: 2 913 917 Dec 2 1956

from saline treated or control animals Histologic differ ences were distinct The weight size and gross appearance of the spleen of polycythemic mice are simple indexes of ery thropoietic effect of an unknown plasma

In polycythemic mice and hypophysectomized rats rectic



F g 59 — Eff ct f p ted 0 5 int venous inject on f a m d n rmal bb t pla m on ticulocyte v l f m that ecei ed nt peritoneal ject ons f pla m b g n ng on me d y that t a f f poly yth mi we t t d (Cou t y f J b L. O *et al* P oc Soc Exp B l & M d 94 243 249 F bru y 1957)

ulocyte determinations in the peripheral blood are equally or more sensitive than radioiron incorporation into red cells in measuring the response to anemic plasma

Erythropoietic Stimulating Effects of Plasma Extracts from Anemic Human Subjects Various types of anoxia evoke the production in laboratory animals of circulatory factors able to stimulate erythropoiesis Few studies have attempted to assess the erythropoietic (EP) properties of body fluids of human subjects Sam J Piliero Paul T Medici Ben Pansky A Leonard Luhby and Albert S Gor don[3] (New York) studied the EP properties in rats of ex tracts of plasma and one of urine from patients with Cooley s anemia and sickle cell anemia

In all instances increases in red blood cells hemoglobin and hematocrit values occurred in rats receiving the plasma filtrates of patients with Cooley s anemia Similar EP stim

(3) P oc Soc Expe B l. & Med. 93 30 305 Novembe 1956

Huggins has shown that the distal low temperatures of the normal ex tremities of rabbits are associated with hypocellular marrows Arterial disease would have the effect of lowering *both* oxygen supply and tem perature and thus the local ratio of oxygen supply to oxygen demand might be less than that to be expected from the decrease of blood flow alone —Ed]

Studies on Erythropoiesis Part IV Reticulocyte Response of Hypophysectomized and Polycythemic Rodents to Erythropoietin Removal of the rat pituitary results in de creased erythropoiesis and reduced metabolism but no change in red cell mass Administering plasma from normal or hypophysectomized animals made anemic by bleeding or phenylhydrazine produces an increase in incorporation of radioiron into red cells of the hypophysectomized recipients L O Jacobson E Goldwasser L F Plzak and W Fried (Univ of Chicago) describe the effect of transfusion induced polycythemia in mice on erythropoiesis and the ef fect of hypophysectomy in rats Radioiron incorporation and reticulocyte levels are compared as a measure of erythropoie sis in recipient animals

Plasma from anemic rats or rabbits was injected into the tail veins of the recipient rats or mice Mice were made poly cythemic by intraperitoneal injections of washed homolo gous red cells Rats were hypophysectomized at 26-28 days or at 2 months

In 26 28 day old rats reticulocyte counts were about 13% on the day before hypophysectomy During the next 5 days the hypophysectomized and sham operated rats had com parable reticulocyte counts but by 4 weeks the counts in the hypophysectomized rats was less than 2% The decline in reticulocyte levels was more rapid in the older group of hy pophysectomized rats When plasma from anemic rats was injected the reticulocyte counts rose in the hypophysecto mized rats whereas untreated controls remained unchanged In polycythemic mice the reticulocytes fell to base line levels in 6 days The injection of plasma from anemic rats or rab bits prevented the fall in reticulocyte counts that occurred in control polycythemic mice that received normal rabbit (or rat) plasma or saline (Fig 59)

At autopsy the polycythemic mice that received anemic plasma had spleens that were at least twice the size of those

(2) Proc Soc Exper Biol. & Med. 94 243 249 February 1957

moval of seven eighths of the liver or removal of adrenals spleen pancreas stomach or intestines from the rat did not lessen the response to an injection of cobalt

After bilateral nephrectomy neither rats nor rabbits could respond to a single dose of cobaltous chloride or a single massive hemorrhage by elevation of plasma erythropoietin Plasma obtained from the blood of nephrectomized rats withdrawn 10-12 hours after injection of cobaltous chloride or after bleeding contained no erythropoietic activity as measured by the incorporation of Fe^{59} into the erythrocytes of starved or hypophysectomized rats A minimum of 5 rats

EFFECT OF NEPHRECTOMY ON ERYTHROPOIETIN PRODUCTION IN RATS

Condition of donor	Stimulus	Assay of plasma (percentage of Fe^{59} incorporated into RBC)
Normal	Cobalt	9 8
Nephrectomized	Cobalt	4
Ureters ligated	Cobalt	5 5
Control	(Saline)	6
Normal (hematocrit)	Bleeding	15 4
Nephrectomized (hematocrit 33)	Bleeding	6 0
Adrenalectomized (hematocrit 3)	Bleeding	11 3
Control	(Saline)	6 9

composed each group shown in the table Similar results were obtained when the erythropoietin titer was measured by the reticulocyte response in mice with transfusion induced polycythemia

These observations indicate that the rate of erythropoiesis or taken as a whole the dynamic equilibrium of the erythron is controlled by the amount of circulating erythropoietin *and that its production in the kidney is determined* by the oxygen supply demand relationship of the body The authors suggest that the metabolic pattern of the normal animal is determined by many factors but chiefly perhaps by the endocrine glands Once the metabolic level is established the dynamic equilibrium of the erythron is automatic but it will respond to various stresses of a normal or abnormal physiologic nature that affect the oxygen supply demand relationship or that interfere with production or utilization of erythropoietin

► [No area of research in hematology today *presents more conflicting*

ulating activity as judged by the reticulocyte and marrow response was revealed in the extract of plasma from 1 of 2 patients with sickle cell anemia The extract of urine obtained from a child with Cooley s anemia also stimulated erythropoiesis

The EP factor detected by the authors is heat stable and can be recovered in boiled filtrates of the plasma and urine In these respects it resembles the material present in the plasma of rabbits and rats with hemolytic or hemorrhagic anemia The activity of human circulating erythropoietin seen in some patients is actually greater than that detectable in any of the bled or phenylhydrazine treated animals examined by the authors Hemoglobin production usually is not stimulated as much as red cell proliferation resulting in a lowered corpuscular hemoglobin content

Since the blood of subjects with Cooley s anemia displays strong EP stimulating qualities and their marrows reveal marked erythroid hyperplasia it seems unlikely that a contributory factor to this condition is reduction in production or use of the EP factor Undoubtedly the more basic etiology centers about the abnormal hemoglobin and hemolytic mechanisms characteristic of these diseases The absence of EP activity in the plasma extract of the patient with severe chronic hypoplastic anemia was significant Perhaps there is an impaired capacity of such subjects to elaborate the EP principle If so administration to these subjects of purified erythropoietin preferably from human sources would be justifiable therapeutically

► [Although Bethell also finds erythropoietic activity in filtrates of the plasma of anemic and polycythemic patients Erslev and Stohlman are unable to detect activity in plasma filtrates from bled animals —Ed]

Role of Kidney in Erythropoiesis The dynamic equilibrium of the erythron is controlled by the relation of oxygen supply in the tissue to demand for oxygen rather than by either alone L O Jacobson E Goldwasser W Fried and L Plzak[4] (Univ of Chicago) reported before that rats which had hypophysectomy thryoidectomy splenectomy adrenalectomy and gonadectomy retained the capacity to respond to repeated phlebotomy with an increase in the plasma content of erythropoietin comparable to that observed in similarly bled normal animals Further it was found that re

(4) N tu e London 179 633 634 Ma 3 1957

It is suggested that the Diego factor be considered part of a new blood group system (the Diego system) classified as the tenth firmly established blood system

► [Hematologic support for the Asiatic origin of Indians in Canada and Venezuela —Ed]

Agglutination and Sensitization of Red Cells by Metallic Cations Interactions between Multivalent Metals and Red Cell Membrane was studied by James H Jandl and Richard L Simmons[6] (Harvard Med School) A prominent feature of the reaction between red cells and most antibodies developed against them is the development of agglutinability which can be elicited under certain conditions Agglutination in vivo appears to initiate the destruction of red cells by nonhemolytic antibodies to red cells in dogs and man Over the years apart from antibodies many substances have been observed to agglutinate normal animal or human red cells either by direct action or after the addition of serum

The authors found that many multivalent metallic cations agglutinate washed red cells Agglutinates so produced are not visibly distinguishable from those caused by complete antibodies The capacity of a metal to agglutinate red cells is restricted to the cationic form and is roughly proportional to the ionic charge Agglutination results from attachment of the metallic cations to the red cell membrane This attachment is dependent in degree on pH ionic strength nature of the anion and presence of inhibiting substances particularly polycarboxylic acids and other metal binding agents including proteins

Several metallic cations are capable of attaching proteins to the red cell surface thus sensitizing the cells to the agglutinating action of serum prepared against the involved protein (e g to agglutination by Coombs serum) This effect was observed with Cr^{+++} Fe^{+++} Be^{++} Th^{++++} and Al^{+++} and irregularly with Cu^{++} provided the metal and protein were added to the red cell suspension within a few minutes of each other Red cells made Coombs positive by metalloprotein complexes behave in vitro and in vivo much as do cells sensitized with incomplete antibody In a system involving washed red cells $CrCl_3$ and 1% human serum albumin in which a 4+ Coombs test was pro

(6) B t J H m t 3 1938 J y 19 7

experimental findings than do the reports concerning the so called erythropoietic factor We completely agree with the authors concept of the dynamic control of normal erythropoiesis as a function of the oxygen supply to oxygen demand ratio of a tissue But what tissue? A priori unless the release of erythropoietic factor by tissue hypoxia is merely a booster mechanism the kidney would seem to be an unlikely organ because of the lability of its blood flow compared for example with that of the bone marrow Erslev has shown that uremia inhibits both production and effect of erythropoietic factor in rabbits There is perhaps then only a brief interval during which the comparative production of the factor in nephrectomized and ureter ligated animals can be assayed We are not yet sure that Dr Jacobson and his associates have proved their case and prefer to await such confirmation before editorial acceptance and acclaim of a conclusion which is of such great potential interest—Ed]

Diego System—Steps in Investigation of New Blood Group System Further Studies In 1954 an antibody was found in the serum of a Venezuelan woman which reacted in the indirect antiglobulin test with the red cells of her baby who had hemolytic disease This antibody reacted also with her husband s red cells but failed to react with 200 random group O bloods Originally this new factor was classified among the private or family blood groups

Since the Indians of the American continent are considered anthropologically direct descendants of Mongolian people from the Old World Miguel Layrisse and Tulio Arends[5] (Caracas) felt that studying the incidence of the Diego factor in other Mongolian branches was important to disclose if this antigen is restricted to the Indians or common to Mongolians Therefore it was studied in various Mongolian Caucasian and Negro populations In 6 South American Indian stocks 1 Canadian Indian stock and 2 groups of Asiatic Mongolians its incidence was high In Caucasians tested results were negative In 2 groups of Venezuelan Negroes with probable Indian admixture the factor was also present

The Diego antigen was inherited in a single dose (heterozygous) in 41 families studied and could be followed through several generations with no sex linkage The first samples of anti Diego serum reacted only in the indirect antiglobulin test to a titer between 1 256 and 1 512 The enzymes papain and trypsin gave no advantage It was more active at room temperature (25 C and 37 C) than at low temperature (4 C and 18 C) The most suitable pH range was 5 8

(5) Blood 12 115 122 F bru ry 1957

layer phenomenon if allowed to stand with formation of a supernatant fraction of cells above the packed erythrocytes These cells remain suspended in the plasma for many hours This superior fraction on a column of blood has a high per centage of reticulocytes and cells with coarse basophilic stippling The direct Coombs test is positive in the superior fraction of such a column as a result either of (a) preferen tial retention of globulins on the membrane of reticulocytes or of (b) preferential damage of reticulocytes by lead and ad hesion of globulin groups to the cell membrane The positiv ity decreases as the sampling approaches the bottom In many instances the whole blood direct Coombs test may be negative and the cells from the superior portion of the col umn strongly positive The latter phenomenon was found in asymptomatic workers exposed to lead in a smelting plant

► [For an account of the basic mechanisms by which metallic cations in vitro may produce a positive Coombs test the reader should consult the preceding article by Jandl and Simmons It is of interest that they were unable to demonstrate such an effect with lead salts in vitro —Ed]

Biologic Interaction between Lymphocytes and Other Cells was studied by J G Humble W H W Jayne and R J V Pulvertaft[8] (Westminster Med School London) in se rum agar cultures using phase contrast time lapse cine micrography The culture method provides a plane surface of solid nutrient medium on which the cell inoculum is placed and is pressed down by a sealed cover slip Over 1 000 specimens (at least 4 preparations of each) of human and murine bone marrow lymph nodes pleural and ascitic fluids and primary and secondary malignant tumors were examined

All tissues examined contained lymphocytes These cells pass freely in and out among other cells until they come on a malignant cell or a megakaryocyte The only other cell for which they show affinity is one undergoing mitosis Lym phocytes do not appear to be attracted to malignant cells or megakaryocytes in the sense that polymorphonuclear neu trophils are attracted to bacteria They wander at random but when they actually touch these cells they often exhibit two distinct types of behavior They move freely around the perimeter of a cell for hours and they appear to attach themselves to the surface of a cell and remain there indefi

(8) Brit J Haemat 2 283 294 July 1956

duced but no agglutination the ratio of Cr^{++} albumin on the surface of the red cells was 2000 1 The metallic cations which agglutinate or which sensitize red cells to agglutination by Coombs serum differ strikingly from those which support hemolysis by complement The cations that induce both phenomena are inversely active in each system

When metalloprotein complexes are formed on red cells the quantity of metal attached to the red cell and required to cause frank agglutination is increased almost 10 fold over that required for a similar degree of agglutination in saline In this sense sensitization of red cells with serum protein is a protective phenomenon analogous in certain ways to the stabilizing effect of proteins adsorbed on colloidal particles

► [A basic study with such clinical overtones as the production in vitro by nonimmunologic means of a positive Coombs test often regarded as a hallmark of autoimmune hemolytic disease —Ed]

Direct Coombs Test in Lead Poisoning One phase of the anemia seen in clinical lead intoxication is attributed to an increase in mechanical fragility of the erythrocytes and an increased rate of hemolysis This change is produced by chemical action of the lead salts on the external lipoprotein envelope of the erythrocytic membrane leading to microscopic denaturization with a loss of elasticity in the membrane The transfusion of such cells into a normal recipient and the determination of their life span using the Ashby technic showed that the damaged cells are removed from the circulation in a random manner and that the cellular defect is retained after transfusion into a normal recipient

A second etiologic mechanism associated with the anemia of lead intoxication is interference in the normal production of ferrous protoporphyrin The blockade is detected by demonstrating an increase in the free protoporphyrin coproporphyrin and uroporphyrin in mature erythrocytes

Donald A Sutherland and Anna M Eisentraut[7] (Dallas) with the technical assistance of Marie Minster found that anemia produced by lead intoxication in humans as well as experimentally induced lead poisoning in dogs results in a positive direct Coombs test The direct antiglobulin test becomes positive within 24 hours in cases of severe lead poisoning produced experimentally in dogs

The blood from dogs with severe lead poisoning forms a

(7) Blood 11 10 4 1031 N embe 1956

tracted to it and moves across the uniting bridge of cyto plasm just before cell division

Attraction of lymphocytes for malignant tissue often leads to their inclusion inside or under vacuoles which form in the malignant cells (Fig 60) and they remain apparently in carcerated in these cells without damage to them or to their host The similar affinity between megakaryocytes and lymphocytes is strange as mitosis has not been observed in megakaryocytes No cell other than the lymphocyte has these properties

The lymphocyte therefore functions in malignant disease as an agent hostile to the host since normally it furthers the processes of growth and division of all cells regardless of their nature It is significant that in serum agar preparations 90% of the cells of inoculated primary tumors died in an hour whereas from secondary new growth in lymph nodes and bone marrow over 90% of the malignant cells survived

This relation of lymphocytes to other cells has not been observed in fibrin clot cultures in slide preparations or roller tubes but the optical conditions of agar culture are so much more convenient that true comparison is impossible

Granulomatous Lesions in Bone Marrow By making par affin sections of bone marrow aspirations Gertrude L Pease[9] (Mayo Clinic) has been able to establish the diagnosis of granuloma in 150 patients Alternate sections were stained with hematoxylin and eosin and the others kept for special staining of bacteria or fungi if indicated The most common ly associated clinical diagnoses were tuberculosis (19) in fectious mononucleosis (16) malignant lymphoma (15) hepatic disease (11) sarcoidosis (9) histoplasmosis (6) and brucellosis (3) Unless a specific organism can be identi *fied in a granulomatous lesion there are no microscopic fea* tures diagnostic of a specific disorder

Marrow aspiration in 7 patients with histoplasmosis re vealed granulomatous lesions in 6 which were prominent and numerous and contained Langhans giant cells Necrosis was observed in all but 1 Organisms were seen on direct ex amination of smears and sections in 2 Cultures of the mar row in 4 patients grew the specific fungus in 3

Bone marrow aspirations in 56 patients with tuberculosis

(9) Blood 11 720 734 A gu t 1956

nitely In many cases the lymphocytes appear to be actually inside cells The nucleus of the investing cell is pressed to one side and lymphocytes circulate for hours never leaving the invested cell s margin Sometimes only one lymphocyte is thus confined in a relatively large space more often the whole space is crowded with freely moving lymphocytes

The authors summarize the functions of the lymphocyte in the following manner The lymphocyte is a mobile source



F g 60—Lymph node second ry d po t f apl t c oma f lu g a cum ul t n f lymphocyt o nd cu l t d mal gn t ll d c d f m ×350 (Cou t sy f H mbl J G t l B t J H m t 2 283 294 J ly 1956)

of enzymes or metabolites which are particularly in demand by a central factory as the endocrine glands is not feasible by actively growing and dividing cells Production of these as need for these substances is focal and intermittent Thus lymphocytes tend to accumulate in areas of repair in bone marrow and around or even inside malignant cells

The lymphocyte usually moves at random but adheres only to cells for which because of their peculiar metabolic activity it has an affinity However when it arrives within not more than 100μ of a cell in mitosis it is actively at

therapeutic agents and the increased use of chemicals the problem of hemopoietic toxicity has become serious Pancy topenia may occur any one of the three elements may become depressed or occasionally hemolytic anemia may be encountered

√The agents associated with leukopenia and granulocyto penia are aminopyrine thiouracil propylthiouracil methyl thiouracil and sulfadiazine Those associated with thrombo cytopenia and purpura are sulfonamides serdomid quinidine quinine gold salts and organic arsenicals Hemolytic anemia has been reported to occur after treatment with sulfonamides quinine pamaquine primaquine aminosalicylic acid pheno thiazine amphetamine mesantoin and stibophen

The history is usually the same A therapeutic agent is given to a patient in customary doses No deleterious effect is expected or observed After the drug has been given again one or more times sore throat purpura weakness pallor or related manifestations appear and hematologic study reveals the abnormality Time interval between administration of the drug and development of the changes varies from a few days to a few weeks and occasionally the side effect occurs with the first known exposure to the drug Quantity of drug appears to be unimportant

Some of the drugs which may produce agranulocytosis oc casionally in man may be the cause of symptoms and signs considered idiosyncrasies such as rash urticaria edema and asthma The untoward reaction to these drugs suggests a sensitization process

In thrombocytopenia the combination of the drug and the platelets probably serves as the antigen and the presence of both is required for agglutination and lysis by the antibody present in the plasma [see article by Bolton this YEAR BOOK p 328—Ed] The action is quite specific and quinidine sensitive individuals have been given the levorotatory isomer quinine without ill effect However in other patients quinine can produce thrombocytopenia itself by the same mecha nism An antigen antibody type of reaction also occurs in agranulocytosis [see article by Moeschlin and Wagner 1953 54 YEAR BOOK p 306—Ed] In sensitive persons a sub stance is found which agglutinates homologous and heter ologous leukocytes in vitro In vivo destruction of aggluti

showed granulomas in 19 Lesions were prominent in 16 Langhans giant cells were observed in 13 and necrosis was seen in 12 Of the 6 patients whose marrow was cultured 3 grew Mycobacterium tuberculosis In 3 who had Ziehl Neelsen stain of the marrow 2 showed acid fast bacilli

Of 21 patients with sarcoidosis granulomatous lesions were seen in the bone marrow of 9 prominent in 6 and containing Langhans giant cells in 3 Necrosis was not seen Of 221 patients with malignant lymphoma granuloma was seen in 15 an incidence of 7%

Thus about 40% of patients with histoplasmosis tuberculosis or brucellosis show granulomatous lesions in bone marrow The lesions are prominent in about two thirds of these patients and Langhans giant cells are seen in more than half About 70% of those from patients with tuberculosis or histoplasmosis will have necrosis Necrosis is rare in other granulomas

Granulomatous lesions in the bone marrow generally tend to be more prominent and Langhans giant cells more numerous in patients with disorders commonly associated with a granulomatous process With one exception necrosis was confined to patients with histoplasmosis or tuberculosis

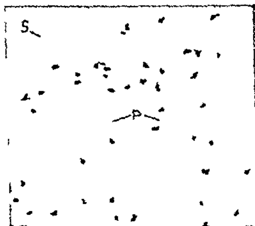
Granulomas have been observed in various disorders for which no explanation is apparent These lesions resemble those in known granulomatous diseases although the incidence of prominent lesions with Langhans giant cells is less Granulomatous bone marrow lesions may represent part of a systemic granulomatous disorder of unknown cause Some patients had histories of previous granulomatous disorders which occurred years before the bone marrow was studied Present lesions in these patients may represent residua of previous diseases and may explain some of the findings in the miscellaneous and indeterminate groups

Blood Disorders Caused by Drug Sensitivity are reviewed by M M Wintrobe and G E Cartwright[1] (Univ of Utah) The first case of agranulocytosis was recorded in 1922 and the sudden appearance and growing number of cases corresponded with the introduction of certain coal tar derivatives as therapeutic agents Later new cases appeared with the advent of new drugs With the ever increasing number of

(1) A M A A h I t. Med. 96 559 566 N mbe 1956

show conspicuous inclusion (Heinz) bodies thought to be the result of damage to cell membrane and hemoglobin sometimes by oxidant drugs In one syndrome originally described by Willi in 1947 the Heinz bodies appear to be formed as a result of inborn error of erythrocyte metabolism manifest as or associated with decreased erythrocyte catalase The patients usually show other congenital abnormalities and the disease is persistent and usually fatal [see Fig 62 in next article —Ed]

The other Heinz body anemia occurs only in premature



F g 61 —P ph ral blood h w g Hei in l on bod in most eryth ocytes 2 poikilocyt (P) and 1 m osph ocyte (S) Brill ant yl bl stain ed ed f om ×500 (Court y of Allison A. C. Brit. J H emat 3 1 18 J n ary 1957)

infants and was first described by Gasser and Karrer in 1948 The characteristic sequence of events is as follows The child is premature but not congenitally defective The peripheral blood film at birth is normal For a hemorrhagic manifestation intensive Synkavit® treatment is initiated Large numbers of Heinz inclusion bodies appear in the erythrocytes during the first few days (Fig 61) then slowly disappear leaving erythrocytes of impaired viability distorted and fragmenting They are cleared from the peripheral blood in the course of about 2 weeks provided that the child survives the original severe hemolytic episode The prospects of com

nated leukocytes probably occurs in the lung capillaries The observed scarcity of juvenile and segmented neutrophilic leukocytes in bone marrow can be explained by a precipitate depletion and exhaustion of the marrow as the result of the greatly increased peripheral destruction of the granulocytes [or by a local agglutinative effect in the marrow —Ed]

A somewhat similar mechanism may be involved in some cases of hemolytic anemia perhaps by interaction of the agent (e g Fuadin®) with the red cells and production of antibodies against the chemically changed cells [see article by Harris this YEAR BOOK p 246 —Ed] In other cases the susceptibility to hemolysis (e g with pamaquin) resides in the subject s erythrocytes The older cells are apparently subject to a wearing out of the mechanisms for maintaining an adequate level of glutathione in red cells [see article by Beutler this YEAR BOOK p 248 —Ed] The pathogenesis of aplastic anemia remains obscure

Unfortunately these sensitizing drugs are often employed when there is little indication for their use Physicians must avoid indiscriminate use of therapeutic agents The potential danger of the drugs in use today must be realized A subcommittee of the A M A Council on Pharmacy and Chemistry s Committee on Research is now attempting to devise a reporting and warning system The danger of self medication must be impressed on the public However the rare untoward effects of various agents should not prevent their use when specific indications exist and no agent is available which is less toxic

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HEMOLYTIC ANEMIAS

Acute Hemolytic Anemia with Distortion and Fragmentation of Erythrocytes in Children A C Allison[2] (Radcliffe Infirm Oxford England) observed 9 children with acute hemolytic anemia associated with contraction distortion and fragmentation of the circulating erythrocytes This picture appears to result from three distinct pathologic processes In two which are seen in newborn infants the erythrocytes

(2) Brit J Haemat 3 1 18 January 1957

S Varadi and E Hurworth[3] (Sheffield England) report on 2 patients with spontaneous Heinz body anemia One a full term twin of normal birth weight had hemolytic anemia and jaundice The other a premature infant had typical hematologic findings but no jaundice Both responded well to a single transfusion

In differential diagnosis of jaundice in the newborn Heinz body anemia should always be considered especially if jaun



F g 62—Num d tort d ed ll d few ph ocyt d d f om 1200 (Co rt y f V r d S d H rworth E Brit M J 1 315 318 F b 9 1 57)

dice—not obstructive in character—develops after the 1st day of life the Coombs test is negative and no immune antibodies are present in the maternal serum It also appears that Heinz body anemia can be present without clinical jaundice If marked anemia develops in a premature infant during the 2d or 3d week and contracted irregularly crenated erythrocytes are found in the smears Heinz bodies should be looked for

► [These patients correspond to those of the first group described by Allison in the preceding abstract—Ed]

Congenital Nonspherocytic Hemolytic Anemia Two Non familial Cases with Red Cell Survival Studies During the past several years this type of anemia has been separated from the previously identified groups of congenital hemato-

(3) B t M J 1 315 318 F b 9 1957

plete recovery are good but there is a danger of kernicterus Synkavit® is an auto oxidizable substance which liberates hydrogen peroxide and induces the formation of Heinz bodies and hemolytic anemia in animals In man also oxidant compounds related to the vitamin K analogues are known to produce severe hemolytic anemias of the Heinz body type Another factor which may increase the predisposition of premature newborn infants to hemolysis is the low level of vitamin E in the plasma

The authors describe 6 patients with a third syndrome which occurred in older infants and children and perhaps resembles a condition recently described by Gasser *et al* as a fatal hemolytic anemia with poikilocytosis and renal failure Heinz bodies did not appear Onset of the disease was sudden The patients became pale and jaundiced most of them vomited and 1 had convulsions There were no characteristic physical findings The hemoglobin level was low and reticulocyte count increased Peripheral blood showed polychromasia contracted distorted and deeply stained erythrocytes and often spherocytes Coombs test was negative The platelet count was considerably reduced The urine contained protein and sometimes hemoglobin erythrocytes and granular casts as well Blood urea level was usually high Unlike thrombotic thrombocytopenic purpura in adults which is said to be invariably fatal the syndrome in children may manifest itself in any degree of severity In 2 patients who died multiple platelet thrombi were noted in the kidneys and other organs Some children recover spontaneously and completely

Heinz Body Anemia in Newborn The condition usually *develops during the 3d week of life after jaundice* The infants become pale drowsy and refuse feedings Examination of the blood before development of anemia shows Heinz bodies in 9 45% of the red blood cells There are many distorted disintegrating red cells when anemia is severest (Fig 62) Heinz bodies are intracellular inclusions in the red cells which stain by various supravital dyes but not by Romanowsky stains They are thought to be particles of denatured hemoglobin and occur in man as a result of poisoning with a variety of chemicals No such cause was discovered in the mothers or infants environment

cytosis in these patients it is not certain that the macrocytosis was not a function of the immaturity of some of the cells in the peripheral blood [In acute experimental hemolytic anemia macrocytosis correlates well with reticulocytosis —Ed]

The presence of increased fecal urobilinogen reticulocytosis and abnormal red cell survival studies indicated a continued hemolysis In 1 patient low serum iron and increased erythrocytic protoporphyrin were noted Heavy metal poisoning was not present The punctate basophilic stippling in the erythrocytes was shown not to be iron This is characteristic of a chemical iron deficiency despite the apparent and documented excessive hemolysis in which case the reticuloendothelial system must retain iron deposits in a particularly insoluble form Conceivably such a hemosiderin complex could remove completely from the metabolic pool a disproportionate share of iron and make the total system iron deficient

The capacity of the body to clear iron tagged with radioactive iron was studied in 1 patient Complete disappearance from the plasma of the radioactivity as early as 2 hours after injection was noted The accelerated rate of removal of this tagged iron globulin complex reflects increased utilization by the hyperplastic erythroid system

Evaluation of Rh Hapten A fraction of human red blood cells can inhibit the agglutinating properties of anti Rh serum This fraction named Rh hapten adsorbs antibody from the anti Rh serum A hapten is a substance which when combined with a suitable carrier can stimulate antibody production in a host and can alone react specifically with that antibody By itself without a carrier it cannot produce antibodies Bettina B Carter A C Williamson Joseph Loughrey and C H Ingram Jr [5] have used this fraction therapeutically in 135 Rh negative sensitized women

These women had previously lost erythroblastotic babies but after treatment with Rh hapten during pregnancy 53% had normal infants There were no cases of demonstrable kernicterus No baby was lost if treatment was begun before a new pregnancy was initiated and continued with daily injections from the time pregnancy was suspected until term

(5) Am. J Obst. & Gynec 72 655 659 S pt mbe 1956.

logic disorders It is characterized by macrocytosis basophilic stippling (Fig 63) hepatosplenomegaly and neonatal jaundice Typically onset occurs in infancy and may simulate erythroblastosis fetalis With the available technics of hematologic analysis the disorder can be differentiated from thalassemia familial spherocytosis the hemolytic diseases based on molecular abnormalities of hemoglobin and acquired hemolytic disease

W Krivit R T Smith J F Marvin R Read and R A Good[4] (Univ of Minnesota) report the disease in 2 children

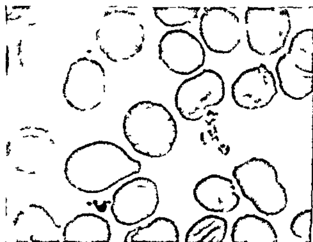


Fig 63 —Basophilic stippling of erythrocytes and normoblastic hyperplasia (Courtesy of Krivit W et al J Pediat 49 245 255 September 1956)

In both it began in infancy and was due to a moderate or severe hemolytic process The laboratory features ruled out thalassemia sickle cell disease and acquired hemolytic anemia There was no hereditary pattern Radioactive Cr^{51} red cell survival studies established an intracorpuscular defect as basis for the disorder However evidence was obtained that in these patients as in others whose disease is due primarily to an abnormality of the red blood corpuscles extracorpuscular factors may contribute to the total hemolytic process

Macrocytosis has been reported by others Because of the relatively large size of immature red cells and the reticulo

(4) J Pediat. 49 245 255 September 1956

charged at the same pH in trypsin digests of hemoglobin A This agrees with the higher net positive charge of the parent protein hemoglobin S There is also a small change in chromatographic behavior of the peptide Corresponding pairs of all the other peptides show similar behavior in these separating systems and therefore probably have similar constitutions

► [Another step in the understanding of what Pauling has termed a molecular disease.—Ed.]

Sickle Cell Anemia in Pregnancy Review of Literature with Additional Case Histories To date 129 cases of sickle cell disease have been reported in pregnant women Morris I Eisenstein A Charles Posner and Stanley Friedman[7] (New York) report 9 additional cases Sickle cell anemia or disease is a hereditary, chronic disease of Negroes with protean manifestations involving virtually every system of the body It is characterized by marked anemia increased red blood cell destruction and sickle shaped red blood cells The sickle cell trait has no clinical significance since there is no anemia or red blood cell destruction The disease usually is manifest during childhood and most patients die at about the 4th decade

Sickle cell crises usually fall into a pattern of febrile arthritic, cardiovascular, neurologic or pneumonic None of these has any pathognomonic symptoms or signs and differentiation from common diseases is difficult Hepatosplenomegaly is fairly constant The disease can simulate almost any condition It should be considered in every Negro who has any type of symptoms Absolute diagnosis depends on demonstration of sickle cells [in fixed smears and the presence of much S hemoglobin on paper electrophoresis —Ed] associated with the clinical manifestations

Sickle cell disease is associated with a high fetal wastage (Table 1) Labor is not affected and most deliveries are normal and spontaneous Maternal infections respiratory genitourinary and puerperal are frequent but are readily controlled with antibiotics Toxemias of pregnancy occur in 10% an incidence slightly higher than normal There is no good evidence that pregnancy is deleterious in sickle cell disease or that women with the disease are relatively infertile but

(7) Am J Ob t & Gy ec 72 6 2 634 S pt mbe 1956

There were no reactions to the injections except for local discomfort

If the fraction is given when the woman first becomes sensitized to Rh before an infant has been lost erythroblastosis may be avoided in that pregnancy and in subsequent pregnancies provided treatment is given each time Labor should not be induced early unless reasons other than Rh sensitization make it imperative With intelligent use of Rh hapten plus exchange transfusions erythroblastosis fetalis should be eliminated as a cause of fetal and neonatal mortality

► [A strong statement and probably not yet justified because of the relatively low and somewhat capricious serial incidence and severity of erythroblastosis. In Diamond s experience exchange transfusion *alone* given within 24 hours of delivery results in a less than 10% mortality and no kernicterus Mothers of a single stillborn erythroblastotic baby may be expected to have a 50% incidence of viable babies even those with multiple stillborn children will subsequently have a 30% incidence of viable babies However if such figures can be shown to be improved by hapten the additional procedure required would be justified —Ed.]

Specific Chemical Difference between Globins of Normal Human and Sickle Cell Anemia Hemoglobin By a two-dimensional combination of paper electrophoresis and paper chromatography which he calls the finger print of the protein V M Ingram[6] (Univ of Cambridge) detected a specific difference in the sequence of amino acid residues of normal and sickle cell hemoglobin confined to one small section of one of the polypeptide chains This is particularly interesting in view of genetic evidence that the formation of *hemoglobin S is due to a mutation in a single gene*

Reasoning on which this study was based is given Action of trypsin on proteins is the most reliable way to split a peptide chain at specific peptide bonds The enzyme attacks only those bonds derived from the carboxyl group of the amino acids lysine and arginine There are about 60 of these in hemoglobin A and S molecules but since it is expected that each molecule is composed of two identical half molecules the number of peptides obtained by action of trypsin should be about 30 with an average chain length of 10 amino acids

Combined electrophoretic and chromatographic examination demonstrated one peptide among the 30 or so which in hemoglobin S is positively charged but which is un

(6) Nature London 178 792 794 Oct 13 1956

tic of S C hemoglobin disease than of S-S disease. Moreover Conley has pointed out the frequency of progressive maternal anemia in S-C hemoglobin disease —Ed]

Confirmation of Structural Abnormality in Stroma of Erythrocytes from Paroxysmal Nocturnal Hemoglobinuria (PNH) after Hemolysis in Distilled Water, described by Matthes *et al* in 1951 is reported by H Braunsteiner E Gisinger and F Pakesch[8] (Univ of Vienna) who cite the theoretical and practical importance of this finding

METHOD —Electron microscopic studies were performed on blood from a woman 30 with PNH at the time of hemoglobinuria and in relative remission Blood from a cubital vein was hemolyzed in 30 parts of distilled water for 3 minutes In some experiments hydrochloric acid or sodium hydroxide was added to vary pH from 6 0 to 8 5 A droplet of fluid containing hemolyzed erythrocytes was transferred directly on formwar membranes for electron microscopic observation and allowed to dry In some instances fixation was first done by adding 1 part of 1% solution of osmium tetroxide to 3 parts fluid.

The stroma of a normal hemolyzed erythrocyte is smooth or slightly granular whereas that from a PNH erythrocyte is patchy as if a coarse precipitation of the matrix had occurred This abnormality was found in approximately 60-70% of hemolyzed red cells from PNH Variation of pH or fixation with osmium tetroxide had no significant effect When PNH erythrocytes were previously centrifuged washed in saline and then hemolyzed differences in stroma structure were less marked

Since no similar change was found in hemolyzed normal erythrocytes or in red cells from iron deficiency pernicious and acquired hemolytic anemias this examination appears to have diagnostic value The negative results reported by Douglas and Eaton may have been due to differences in technic The visible abnormality in the stroma is probably a secondary phenomenon under nonphysiologic conditions The fundamental defect may be lack of an enzyme or presence of an abnormal substance in the stroma which leads to pathologic precipitation of the matrix in distilled water

► [The physiologically important anomaly of the red cells in this condition is susceptibility to lysis by a normal serum factor properdin when the blood pH is lowered Normal red cells likewise behave in this fashion after exposure to tannic acid.—Ed.]

Agglutination of Sensitized Red Cells by Large Anisometric Molecules was demonstrated by James H Jandl and Wil

(8) Blood 11 731 756 August, 1956

30 of 138 died during pregnancy Other abnormal features of pregnancies are shown in Table 2

During the prenatal period hematologic status should be determined weekly and vitamins iron and liver extract given Transfusions are not indicated unless the hemoglobin level is below 8 Gm An infection requires immediate hospitalization ACTH and cortisone have been reported effective in a crisis Oxygen for dyspnea and prophylactic digitalis for impending heart failure may be helpful

There is no evidence that induction of labor when the

TABLE 1—Causes of Fetal Loss

Cause	No
Spontaneous abortions	55
Therapeutic abortions	3
Salpingectomy	1
Mothers died undelivered	11
Stillborn and neonatal deaths	47
Total	117

TABLE 2—Summary of 138 Recorded Cases of Sickle Cell Disease in Pregnancy

	Total No	%
Mothers	138	
Maternal deaths	30	21 7
Total pregnancies	286	
Spontaneous abortions	55	19 5
Viable pregnancies	214	75 3
Surviving babies	*162*	
Dead viable babies	47	
Total fetal loss	117	41 9

fetus is viable results in fetal salvage Labor is managed conventionally Oxygen should be given freely and prophylactic low forceps delivery under pudendal block is desirable Cesarean section is reserved exclusively for obstetric indications not for fetal salvage Sickle cell disease per se is not an indication for therapeutic abortion The high maternal mortality rate justifies sterilization

► (The authors make no attempt to distinguish between sickle cell disease (S S hemoglobin) and some of its clinically significant relatives such as S C hemoglobin disease Actually until after 1950 with the introduction of paper electrophoresis into clinical use this was not feasible However in the review of the maternal deaths cited from the literature subsequent to that time this might be expected Indeed, the authors frequently noted the presence of splenomegaly a finding far more characteris

undissociable chains of red cells are indicative of red cell sensitization

So used PVP was more sensitive as a developing agent than 25% albumin or Coombs serum Red cell abnormalities were revealed by PVP in 3 cases of acquired hemolytic anemia in which the Coombs test was negative or only weakly positive One instance was observed in which red cell sensitization in terms of agglutinability by Coombs serum was completely effaced by 3 standard washings in saline whereas 20 washes failed to reverse the PVP test The sensitivity and simplicity of the PVP test recommend it as a routine hematologic technic

METHOD —Whole blood or packed red cells (0 1 ml) is added to 0 5 ml of 5% buffered solution of PVP with molecular weight of 160 000 The suspension is mixed and permitted to stand at room temperature until settling is evident 15 ml physiologic saline is then added the tube is inverted two or three times and presence of agglutination or of persistent rouleaux is read microscopically Heavy sensitization is visible macroscopically Short chains containing 2 4 red cells is scored as 1+ longer chains and occasional small clumps as 2+ many aggregated rouleaux and numerous clumps as 3+ and coarse macroscopic clumps as 4+

Among plasma proteins the order of decreasing effectiveness in agglutination of sensitized red cells was fibrinogen gamma globulin other globulins and albumin Concentration by 10 20% of whole plasma or of whole serum through pervaporation was sufficient to agglutinate sensitized red cells as were increases in concentration of fibrinogen or of globulin to levels only slightly above the physiologic Such proteins may induce destruction of sensitized red cells in vivo through formation systemically and/or locally in certain organs of red cell aggregates which become sequestered in various capillary beds such as those in the spleen

Note on Effect of Hydrocortisone on Microelectrophoretic Characteristics of Human Red Cell Antibody Unions W P Creger E H Tulley and D G Hansen[1] (Stanford Univ) attempted to elucidate the paradox that ACTH or cortisone may produce marked clinical improvement in human immunohemolytic states without parallel change in red cell sensitization by antibody globulin The method of microelectrophoresis was described before in a study showing that normal electric charge of the naked human red cell could be significantly altered by treatment of the cell with human antie

(1) J Lab & Cl M d. 47 686 690 M y 1956

liam B Castle[9] (Harvard Med School) in studies directed toward determining the physiologic significance of various previously observed in vitro phenomena These findings provide an additional means of demonstrating red cell sensitization which should be useful clinically

Saline solutions of several macromolecular substances e g plasma proteins carboxymethylcellulose polyvinylpyrrolidone (PVP) and dextran agglutinated red cells previously sensitized with incomplete antibody or with metalloprotein complexes Their efficacy in this respect is related

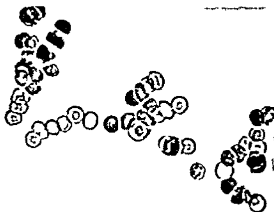


Fig 64 (Court f J dl J H a d C tl W B J Lab & Cl Med 47 669 685 May 1956)

to their ability to produce rouleaux of normal cells this in turn relates to the degree of molecular anisodiametry of the substances

Rouleaux of normal red cells are dispelled by appropriate dilution with saline of the rouleaux producing agents Sensitized red cells however persist in the aggregated state after saline dilution both as rouleaux (permanent rouleaux) and as agglutinates Consequently substances which induce rouleaux can be practically employed in recognition and study of red cell sensitization in hemolytic anemias Figure 64 shows red cells from a patient with acquired hemolytic anemia after suspension for 5 minutes in 1% bovine fibrinogen and resuspension in 10 volumes of physiologic saline The

(9) J Lab & Cl Med 47 669 685 May 1956

sons of Cr^{51} labeled red cells hemoglobin and chromic chloride in saline Data were reported as ratios of body surface over organs to precordial radioactivity Differences characteristic of each were observed and served as a basis for in-

F g 65 —I d t of Cr^{5} label d d ell d struction p t t w th mod t ly se cong tal h molyt mi (h dita y ph ocyt) w att d d by p ed m t uptak f rad oa t vity pl en. Not both eased plen ct vi y t tim d mann in wh h Cr^{5} prog s ly depo ted pl en p oport on t t mov l f om blood st eam (Courte y of J dl J H et l J Cl n l t 35 842 867 A gu t 1956)

terpretation of a study of 11 patients with hemolytic anemias of diverse kinds Measurements made on these patients after injection of Cr^{51} labeled autogenous red cells suggested that progressive accumulation of Cr^{51} in the spleen accompanying the disappearance of Cr^{51} labeled red cells from the blood stream as in congenital hemolytic anemia (Fig 65)

rythrocytic antibodies Measurements were obtained by timing migration of single red cells viewed microscopically in a hollow slide through a field of constant milliamperage and known dimensions

Treatment of erythrocytes with hydrocortisone before or after addition of anti A antibodies to human red cells of group A caused them to migrate at nearly the same speed as naked red cells not treated with antibody If erythrocytes were treated with hydrocortisone alone there was little deviation from migration of the untreated cell though cells moved a trifle more slowly Similar data were obtained with anti CD antibody Despite the rather striking alteration in migration of red cell antibody complex when treated with hydrocortisone i e reversal of the electric charge change wrought on the red cell by antibody action in vitro the direct Coombs test remained positive

There may be marked differences in bonding between red cell and antibody within the framework of a positive direct Coombs test of constant serologic level and these differences may have variable pathologic implications for the red cell This interpretation may be relevant to those cases of immunohemolytic anemia which though treated with steroids with ample clinical success show no change in the titer of the direct Coombs test

Clinical Determination of Sites of Red Cell Sequestration in Hemolytic Anemias The wide application of red cell survival technics has revealed the importance of excessive red cell destruction in the pathologic physiology of many of the anemias An increasing array of in vitro methods for detecting red cell or serum abnormalities has provided insight into the in vivo mechanisms underlying some of these processes In certain disease states the presence of visible or physically measurable alterations of the red cells has permitted detection of the sites and to some extent of the mechanisms of sequestration of these cells Valuable observations have been made on pathologic material from patients with congenital hemolytic anemia and sickle cell anemia

James H Jandl Mortimer S Greenberg Robert H Yonemoto and William B Castle[2] (Harvard Med School) determined the deposition sites of Cr^{51} in the human body by body surface counting after the injection into normal per

(2) J Cl n Invest. 35 84 867 August 1956

ments on the spleen 20 or 30 minutes after the injection of labeled autogenous red cells followed by others a day later and again after the estimated removal of 25 50 and 90% of the labeled cells should provide the desired prognostic information

Sequestration of labeled red cells builds up radioactivity in an organ in approximate proportion to its rate of disappear ance from the blood On the other hand high initial activity over the organ (unless followed at once by rapid accumula tion) signifies a large vascular bed rather than red cell sequestration

Mild or discrete red cell alterations (spherocyte) sensi tized cells and the morphologically peculiar cells encoun tered in pernicious anemia and in Cooley s anemia) lead to sequestration by the spleen presumably due to the refined filtering function of that organ This is attended by little or no release of hemoglobin into the circulation and may be in terpreted a an extravascular process More gross red cell changes such as agglutination or cellular changes which may grossly affect blood viscosity as in sickle cell anemia lead to a more indiscriminate filtration in organs with large vascular beds the lungs and liver as well as the spleen if present and functioning Such widespread red cell trapping especially when not in close relation to concentrations of reticulo endothelial cells may favor the release of hemoglo bin into the plasma and thus simulate the effects of a circu lating hemolysin

► [The numerous figures in the original based on results in individual patients are instructive and there is a section on the radioactive hazards of the procedure —Ed]

Results of Splenectomy in Autoimmune Hemolytic Ane mia were assessed in 28 cases by G Chertkow and J V Dacie[3] (Postgrad Med School London) In 12 of 21 pa tient with idiopathic disease and in 2 of 7 with hemolytic anemia secondary to lymphomas result of splenectomy was good or fair Six whose responses were good remained free of excessive hemolysis or anemia for 8 months to 5½ years One patient with reticulosarcoma died of the underly ing disease 18 months after splenectomy but without recru descence of hemolysis Eight patients whose result was fair showed distinct improvement but hemolysis and some ane

(3) Brit J Haemat 2 237 249 July 1956

indicates active red cell sequestration In determining the extent of this sequestration a simple expression may be used index of sequestration which deducts that radioactivity initially present and due simply to the size of the splenic

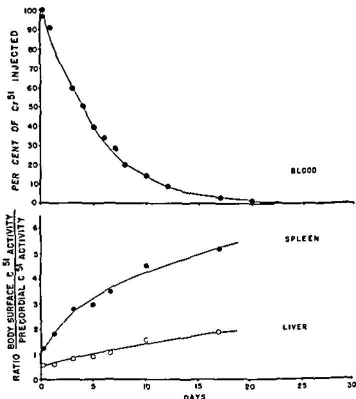


Fig 66—In p t t w th moderately seve e stable id path q ed h molyt c anem a a d ev d ce f d cell s nst t at o approximately 20% of C labeled ed cells we e em d fr m c rc l t on da ly H y accumul t n of Cr^{51} i splee m r red rap d d sappe r f C f om pe ph l blood (Co t y of J dl J H *et al* J Cl In e t 35 842 867 Augu t 1956)

vascular bed from later values obtained over that organ In certain acquired hemolytic anemias the short survival of labeled red cells in the circulation is accompanied by a progressive increase of radioactivity over the spleen (Fig 66) In such patients as in congenital spherocytic anemia the anemia is relieved by splenectomy Radioactivity measure

effect He had been well until 1 month before admission when in testinal symptoms recurred Viable schistosome ova were found and Fuadin® therapy wa started The first four injections were with out incident the fifth caused some reaction and the severe acute hemolytic episode occurred after the sixth injection Examination revealed a rapidly dropping hemoglobin level acholuria abnormally increased plasma hemoglobin methemalbumin and bilirubin and hemoglobinuria Erythrocytes showed reticulocytosis and spherocy tosis with increased osmotic and mechanical fragility and a positive Coombs test Diagnosis was acute acquired hemolytic anemia of so called autoimmune antibody type and cortisone therapy was started Patient made a rapid and uneventful clinical recovery

The patient s erythrocytes gave a positive antiglobulin test Se rum contained a factor(s) capable of (1) agglutinating patient s or normal red cells (2) sensitizing normal red cells so that they gave a positive Coombs test and (3) hemolyzing trypsinized normal red cells or red cells from a patient with paroxysmal nocturnal hemo globinuria in serum which had not been inactivated by heat. None of these activities could be demonstrated unless Fuadin® or the chem ically related sodium catechol disulfonate was added to the reacting systems The Fuadin® requiring agglutinin was passively trans ferred by means of infusion of 300 ml of patient s plasma to a hematologically normal recipient in whom it was detected for 26 days It could be activated in vivo by administration of Fuadin® to the normal recipient producing gross red cell agglutination and sensitization of the normal erythrocytes shown by a positive Coombs test Titer of Fuadin® requiring agglutinin fell abruptly from 1 16 to 1 4

Possibly a chemical such as Fuadin® Mesantoin® or phe nylhydrazine might so alter the surface of the red cell that it would become antigenic by chemical action on the surface proteins by combination with surface proteins or by expos ing deep antigens otherwise presumed hidden but this has not been proved in hemolytic anemias in man An alternate possibility exists that in a sensitized person administration of the drug may induce formation of abnormal proteins and that in special instances in which hemolytic anemia occurs the abnormal proteins have a configuration which confers on them agglutinating or hemolyzing activities directed against erythrocytes It seems as reasonable to conclude that such apparently diverse stimuli as drug sensitivity infections and neoplastic diseases could produce antierythrocyte activ ity through abnormal protein production as by alteration of the antigenicity of the red cell and consequent production of autoantibodies

► [It will be recognized that these observations present a precise analogy

mia persisted Eleven patients apparently received no benefit from splenectomy Of these 7 died with active hemolysis unchecked 1 also had terminal endocarditis 1 terminal sepsis and 2 underlying Hodgkin s disease and chronic lymphatic leukemia respectively These results are less satisfactory than those reported by others In 255 collected cases response to splenectomy in idiopathic cases was considered good in 52% poor in 35% and fair or doubtful in the rest

No reliable clinical hematologic or serologic criteria were found to predict the result of splenectomy Data suggested success might be less likely in younger patients in those most severely anemic in the presence of thrombocytopenia and in patients with relatively small spleens A much larger series is required to verify these impressions statistically A disappointing response to hormone therapy should not on present evidence contraindicate splenectomy conversely failure to respond to splenectomy does not indicate that a patient will not subsequently respond favorably to the hormones

Relatively poor results of splenectomy are thought consistent with the hypothesis that the spleen is only a partial source of autoantibodies that the patient forms and that destruction of red cells affected by these antibodies is not wholly dependent on presence of a spleen Complete (serologic) cure is only possible when autoantibody formation ceases This seldom or never results from splenectomy Antiglobulin tests remained clearly positive after splenectomy in 26 of 28 patients among whom many showed clinical improvement in 2 with good responses the test became negative or doubtfully positive In view of the uncertain results of splenectomy ACTH or cortisone is the treatment of choice in autoimmune hemolytic anemia Splenectomy is recommended only if hormone treatment fails

Studies on Mechanism of Drug Induced Hemolytic Anemia during readministration of Fuadin® are reported by John W Harris[4] (Western Reserve Univ) and provide for the first time evidence that a drug may cause a classic immune hemolytic system to develop

Puerto Rican worker 28 was treated for intestinal schistosomiasis 10 years earlier with a full course of Fuadin® without untoward

(4) J Lab & Cli Med 47 760 775 May 1956.

stable while that of nonsensitive cells is stable Glutathione instability depends on the presence of oxygen and is independent of the hematocrit Protection of the GSH of non sensitive cells requires glucose

Application of this test to the blood of 5 known drug sensitive and 7 drug nonsensitive persons demonstrated the GSH of sensitive cells to be unstable that of nonsensitive cells stable In 159 subjects whose drug sensitivity was unknown incidence and racial distribution of glutathione instability corresponded to the approximated known incidence and racial distribution of drug sensitivity

The hypothesis that glutathione concentration alone governs sensitivity to hemolysis however is untenable The reduced glutathione levels of blood from sensitive persons who had undergone drug induced hemolysis and were temporarily completely resistant to the hemolytic effect of the drug were still abnormally low If GSH serves in a protective capacity nonsensitive cells must have a mechanism which protects GSH and in sensitive cells this mechanism is defective

Structure of Vitamin B_{12} the specific nutrient lacking in pernicious anemia is discussed by Dorothy Crowfoot Hodgkin Jennifer Kamper Maureen MacKay Jenny Pickworth Kenneth N Trueblood and John G White[6] Vitamin B_1 was isolated in 1948 and the presence in the molecule of an atom of phosphorus and one of cobalt was soon recognized By 1950 acid hydrolysis yielded a riboflavin like structure 5 6 dimethylbenziminazole linked to a phosphorylated ribose glucoside Recent progress confirms the authors earlier conclusion that the probable structure of vitamin B_1 is as shown in Figure 67 The porphyrin like hexacarboxylic acid structure surrounding the cobalt atom was isolated from alkaline hydrolysates of the vitamin by Cannon Johnson and Todd in 1954 Detailed x ray analysis indicates that the molecule is beautifully composed and almost spherical with all the more chemically active groups on its surface It is built around the two planes of the central cobalt containing nucleus and the benziminazole nucleus which are nearly at right angles to each other The ribose ring turns in a plane nearly normal to the benziminazole nucleus which permits

(6) N t London 178 64-66 J ly 14 1956

for the red cell to the immunologic systems previously related to platelets for Sedormid® by Ackroyd and to granulocytes for Aminopyrine® by Moeschlin Elsewhere in this YEAR BOOK page 331 a case of Fuadin® induced thrombocytopenia probably involving a similar immunologic mechanism is reported —Ed]

Glutathione Instability of Drug Sensitive Red Cells New Method for In Vitro Detection of Drug Sensitivity is described by Ernest Beutler[5] (Univ of Chicago) Primaquine sulfanilamide acetanilid and Promizole® may induce an acute hemolytic anemia in some persons Earlier studies showed this to be an intrinsic defect of the red blood cell a defect that is rare among Caucasians but occurs in about 10% of American Negroes By standard technics the morphology of the cells is normal they do not sickle nor do they contain any abnormal hemoglobin detectable by paper electrophoresis The antigen pattern is not characteristic and Coombs test is negative Cells are not unusually susceptible to acid hemolysis amount of methemoglobin is normal and mechanical chemical and osmotic fragility is normal

Two differences have been detected in vitro between sensitive and nonsensitive cells When incubated with acetylphenylhydrazine and certain other compounds the sensitive cells form many small scattered Heinz bodies while the nonsensitive cells form only a few slightly larger marginal Heinz bodies Among 104 healthy volunteers false positive tests occurred in only 2 and no false negative tests were noted The test is simple to perform but is quite sensitive to alterations in oxygen saturation of venous blood and must be assessed subjectively and thus has not been satisfactory under field conditions

The other difference is the lower average reduced glutathione level in sensitive as compared to nonsensitive red cells In vivo primaquine administered to a sensitive subject reduces the glutathione content of red blood cells to about half the original already subnormal level This abrupt fall precedes the major portion of the hemolysis and as hemolysis progresses the glutathione again rises to the original level

The in vitro test consists of incubating blood samples with acetylphenylhydrazine at almost complete oxygenation and measuring the level of reduced glutathione before and after incubation The gluta hione (GSH) of sensitive cells is un

(5) J Lab & Clin Med 49 84-95 J n ary 1957

biologic synthesis of vitamin B_{12} in the presence of 125 mg of δ aminolevulinic acid 1 4 C^{14} having a molar activity of 8.3×10^5 count/minute for each active carbon Under fermentation conditions used the culture produced 0 163 mg vitamin B_{12} After the addition of 10 1 mg nonradioactive B_{12} 6 294 mg B_{12} was isolated Molar activity of undiluted B_{12} was 30×10^5 count/minute

On the assumption based on previous studies of porphyrin formation that 2 moles of aminoketone are used for each ring 15 labeled carbon atoms of the porphyrin like structure were hypothetically derived from labeled substrate molar activity of each of these would be 2×10 count/minute representing a fourfold dilution during synthesis of the vitamin It may therefore justifiably be concluded that the porphyrin like structure of vitamin B_{12} is synthesized from δ aminolevulinic acid as are porphyrins and that the mechanism of synthesis of the ring system in the vitamin is similar to that of porphyrins

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PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

Family Study of Pernicious Anemia Sheila T Callender and M A Denborough[8] (Radcliffe Infirm Oxford England) examined 308 close relatives (parents siblings and children) of patients with pernicious anemia and 259 control subjects In addition to anemia and macrocytosis achlorhydria and other abnormalities of gastric secretion were sought Although there was no pernicious anemia among the controls 2 previously undiagnosed cases were found among the relatives both in sisters The incidence of iron deficiency anemia was no greater in the relatives than in controls However macrocytosis was more common among the relatives It was observed even in those with free acid in their gastric secretion In both the relatives and the controls incidence of achlorhydria was low up to age 40 but then increased in frequency with advancing years After middle life the incidence of achlorhydria tended to be higher in the relatives

(8) Brit J Haemat 3 88 106 January 1957

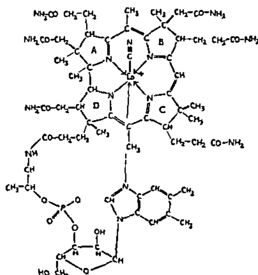


Fig 67 (Court y of Hodgkin D C *et al* Natur London 178 64 66 J ly 14 1956)

easy linking through the phosphate propanolamine and propionic acid residues through ring *D* of the planar group

On Biosynthesis of Porphyrin like Moiety of Vitamin B_1
Recent chemical and x ray studies suggested a probable structure of vitamin B_{12} which contains a porphyrin like structure The structural similarities are sufficient to suggest that the basic mechanism of synthesis of this part of the vitamin is similar to that known for pyrrole and porphyrin synthesis and the modified structure is subsequently methylated in certain positions to form the final product characteristic of vitamin B_{12}

It has been found that active succinate and glycine are the sole precursors of porphyrin compounds in all biological systems The glycine and succinate condense to form α amino β-ketoadipic acid which on decarboxylation yields δ aminolevulinic acid Condensation of *2* moles of the amino ketone forms the precursor monopyrrole porphobilinogen of which 4 moles then condense to form a porphyrin

To check this hypothesis David Shemin John W Corcoran Charles Rosenblum and Ian M Miller[7] did a micro

(7) Science 124 272 A g 10 1956

biologic synthesis of vitamin B_{12} in the presence of 125 mg of δ aminolevulinic acid 1 4 C^{14} having a molar activity of $8\,3 \times 10^5$ count/minute for each active carbon Under fermentation conditions used the culture produced 0 163 mg vitamin B_{12} After the addition of 10 1 mg nonradioactive B_{12} 6 294 mg B_{12} was isolated Molar activity of undiluted B_{12} was 30×10^5 count/minute

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(8) Brit J Haemat 3 88 106 January 1957

than in the controls In addition to achlorhydria some of the relatives had low uropepsinogen excretion gastric atrophy poor absorption of vitamin B_{12} (table) corrected by intrinsic factor and a low or low normal serum vitamin B_{12} level but without symptoms or anemia It is thought that these changes may represent a prepernicious anemia state whether anemia later becomes manifest can only be determined by follow up

The parents of 9 patients with pernicious anemia were investigated Defects of a prepernicious anemia state were seen in 4 5 were normal In 2 families in which both parents were tested 1 parent in each showed abnormalities One of the other parents with prepernicious anemia had a sister

ABSORPTION OF Co^{60} VITAMIN B BY RELATIVES WITH ACHLORHYDRIA

No TESTED	UROPEPSINOGEN EXCRETION	ABSORPTION OF VITAMIN B_{12}
33 Relatives	Normal	Normal
7 Relatives	Low	Normal
4 Relatives	Low	Impaired
12 Relatives	Low	As in pernicious anemia

with the disease the other a cousin It is suggested that these asymptomatic findings represent a carrier state

► [These findings elegantly confirm the suspicion that a hereditary loss of intrinsic factor from the gastric juice usually associated with achlorhydria is an essential prelude to spontaneous pernicious anemia —Ed]

Pathogenesis and Treatment of Macrocytic Anemia Information Obtained with Radioactive Vitamin B_{12} is reviewed by Patricia A McIntyre Marie V Sachs Julius R Krevans and C Lockard Conley[9] (Johns Hopkins Univ) The clinical manifestations of pernicious anemia probably are entirely due to a deficiency of vitamin B_{12} resulting from impaired absorption of the vitamin from the gastrointestinal tract To be absorbed in adequate amounts a substance secreted by the normal stomach the intrinsic factor of Castle must be present The basic defect of pernicious anemia is failure to produce intrinsic factor As a result vitamin B_{12} is not absorbed even though ingested in usual amounts

Vitamin B_{12} can be labeled by adding radioactive cobalt to the medium in which the vitamin is synthesized by microorganisms When 0 5 µg of labeled vitamin is given orally

(9) A M A Arch. Int Med. 96 541 549 November 1956.

to normal subjects most of it is absorbed but in patients with pernicious anemia most of the radioactivity is excreted in the feces This is an effective and reliable method for de tecting impaired absorption of the vitamin but all stools must be collected in toto for at least 6 days If a large amount of nonradioactive vitamin B_{12} is injected parenterally a por tion of the radioactivity absorbed from labeled vitamin pre viously administered orally will be flushed out into the urine The routine test is 0 5 µg radioactive vitamin B_1 orally during the fasting state followed in 1 hour by 1 000 µg nonradioactive vitamin B_1 intravenously In normal subjects about 25% of the orally administered radioactivity appears in the urine in 24 hours representing about a third of the total absorbed In 22 patients with pernicious anemia less than 5% appeared in the urine

The greatest virtue of the test is its ability to detect per nicious anemia even in complete remission as a result of prior therapy After remission has been induced diagnosis may be impossible except by use of the radioactive tracer test Two important factors are the size of the oral dose of the labeled vitamin which should be rigidly standardized in micrograms and the fact that excretion of absorbed radio activity may be impaired in the presence of renal insuffi ciency

Defective absorption due to deficient intrinsic factor alone can be corrected by administering intrinsic factor together with vitamin B_1 When it is due to functional or anatomic derangement of the small intestine as in sprue enteritis pancreatic insufficiency and intestinal resection intrinsic fac tor concentrate does not help When due to parasitic organ isms in the intestinal tract which utilize the vitamin such as fish tapeworm or luxuriating bacteria in blind loop lesions or diverticula of the small bowel destroying the organisms with appropriate chemotherapeutic agents will correct the defect

In 2 patients who had had resection of the small intestine except for about 1 ft of jejunum absorption of vitamin B_1 was severely impaired Thus little absorption of the vitamin takes place in the upper gastrointestinal tract Three patients with regional enteritis had impaired absorption in 1 only about 2 ft of the terminal ileum was involved Therefore a

major site of vitamin B_{12} absorption is the lower small intestine When the radioactive vitamin was instilled into the rectum no detectable absorption occurred

Restricted absorption of vitamin B_{12} even in normal persons makes it obvious that intensive therapy with the vitamin can be effectively accomplished only by parenteral administration

Incidence of Megaloblastic Anemia after Total Gastrectomy According to Lloyd D MacLean and R Dorothy Sundberg[1] (Univ of Minnesota) megaloblastic anemia indistinguishable from pernicious anemia is a late but inevitable sequela of total gastrectomy in patients who have not received prophylactic parenteral vitamin B_{12} or liver extract treatment Megaloblastic bone marrow developed in all but 1 of 11 patients with histologically proved total gastrectomy without prophylactic therapy who survived over 3 years The patient who did not have megaloblastosis lived over 3 years after gastrectomy but underwent no further hematologic examination beyond 2 years and 5 months after operation Only 2 patients displayed megaloblastosis less than 3 years after operation

Total gastrectomy was performed for various diseases including adenocarcinoma of the stomach benign gastric ulcer gastric polyps hypertrophic gastritis cardiospasm and esophagitis Two of 13 patients who have lived more than 3 years after total gastrectomy had received prophylactic therapy Neither has anemia although they are living 11 and 8 years after operation

The megaloblastosis is not related to the blind loop anemia seen in animals and human beings since it follows esophagoduodenostomy as well as esophagojejunostomy It is unlikely that all patients would have had pernicious anemia without total gastrectomy especially since 5 had free hydrochloric acid on gastric aspirations before operation Megaloblastic anemia that follows total gastrectomy responds completely to parenteral vitamin B_{12} therapy Prophylactic folic acid alone is not indicated and vitamins containing it are hazardous because of possible aggravation of the neurologic component of the deficiency Megaloblastosis after total gastrectomy is not believed due to sprue or a nu

(1) New England J Med 254 885 893 May 10 1956

tritional deficiency other than vitamin B_{12} because (1) vitamin B_{12} alone accomplished complete remission (2) gastrectomized patients do not absorb radioactive vitamin B_{12} unless supplied with intrinsic factor (3) many patients with megaloblastic anemia following total gastrectomy display nearly normal nutrition and (4) combined degeneration of the spinal cord is often seen whereas it is lacking in nutritional macrocytic anemia [i e when gastric acidity is present —Ed]

Intrinsic factor production is the only essential function of the stomach in man All patients with total gastrectomy or proximal subtotal gastrectomy with esophagoantrostomy should receive prophylactic parenteral vitamin B_{12} or liver extract therapy at least before 3 years after operation and continuously thereafter The site of intrinsic factor production corresponds to the area of the stomach pathologically involved in pernicious anemia (body and fundus)

► [In the 6 patients with achlorhydria before operation the clinical proof that total gastrectomy per se results in pernicious anemia is clouded by the possibility that "spontaneous" loss of intrinsic factor was in progress However the results in the other 5 patients and especially acute observations such as those of Halsted showing that total gastrectomy promptly abolishes the assimilation of vitamin B_{12} leave little doubt of the indispensability of gastric secretion in this regard.—Ed.]

Intrinsic Factor Studies IV Selective Absorption and Binding of Cyanocobalamin by Gastric Juice in Presence of Excess Pseudovitamin B_{12} or 5 6 Dimethylbenzimidazole Intrinsic factor in normal human gastric juice enhances absorption of cyanocobalamin in patients with pernicious anemia Such gastric juice also binds cyanocobalamin as estimated by microbiologic assay dialysis or paper electrophoresis That binding of this vitamin is not equivalent to intrinsic factor activity appears from several reports but published data indicate that all intrinsic factor preparations bind some vitamin B_{12} Bishop *et al* interpret their recent observations as demonstrating that vitamin B_{12} already bound to intrinsic factor is absorbed preferentially over other added B_{12} They conclude that vitamin B_{12} binding power is necessary for intrinsic factor activity and recent studies confirm this

One moiety contributing to the structure of the cyanocobalamin molecule is 5 6 dimethylbenzimidazole (DMBI) When this portion is replaced by adenine the compound is

known as pseudovitamin B_1 To determine whether this competes with B_1 for the mechanism which effects intestinal absorption of B_1 Mary Bartlett Bunge Lee L Schloesser and Robert F Schilling[2] (Univ of Wisconsin) studied effect of excess pseudovitamin B_1 or DMBI on in vivo absorption of B_1 Co^{60} in 6 patients known to lack intrinsic factor Effect of these compounds on in vitro binding of B_1 Co^{60} by gastric juice or serum was studied by dialysis By a combination of both methods intrinsic factor activity and certain in vitro binding properties of gastric juice were correlated Finally effectiveness of pseudovitamin B_1 as a flushing agent for absorbed B_1 Co^{60} was studied

It was concluded that neither pseudovitamin B_1 nor DMBI competes with radioactive cyanocobalamin for physiologic mechanisms effecting absorption of cyanocobalamin Pseudovitamin B_1 is much less effective than cyanocobalamin in causing urinary excretion of absorbed radioactive cyanocobalamin Similar quantities of pseudovitamin B_1 and cyanocobalamin are retained after injection of 122 µg of either

In vitro binding of cyanocobalamin by gastric juice is a selective process showing a distinct preference for cyanocobalamin over pseudovitamin B_{12} or DMBI The process of cobalamin binding by serum unlike that in gastric juice does not manifest a selectivity for cyanocobalamin in presence of excess pseudovitamin B_1 Electrophoretic mobilities of cyanocobalamin binding substances in normal human gastric juice and in an intrinsic factor concentrate are similar The data are in accord with the hypothesis that binding of cyanocobalamin is necessary for intrinsic factor activity but binding alone is no criterion for the presence of such activity

► [*The experience of Nieweg with labeled vitamin B absorption in gastrectomized rats likewise indicates the importance of binding but only by the proper species of intrinsic factor Rat human and pig intrinsic factor all bind vitamin B but only rat intrinsic factor enhances the absorption of the vitamin —Ed*]

Studies on Vitamin B_1 Binding Principle and Other Biocolloids of Human Gastric Juice were suggested to Ralph Grabeck[3] (Helsinki) by the contradictory reports of others and by the need for an in vitro method of assay for intrinsic factor This normal principle of human and hog gastric juice

(2) J Lab & Clin Med. 48 735 744 N embe 1956
(3) A t med aca d (pp 314) 154 7 87 1956.

which is lacking in pernicious anemia and after total ga trec tomy in man facilitates assimilation of vitamin B_1 from the alimentary tract Pooled frozen neutralized or fresh gas tric juice from healthy young persons was collected by in sulin stimulation Using starch electrophoresis at pH 6 1 Grasbeck confirmed the earlier observations of others show ing several anodically migrating protein components Only 2 of these peaks showed clearcut vitamin B_1 binding The faster migrating peak activity was more heat stable (15 min utes at 70 C) than the slower moving peak which had less affinity for vitamin B_1 The binding capacity of these sub stances for radioactive vitamin B_1 was tested by dialysis or by adsorption with Lactobacillus leichmannii resting cells

Because the faster moving peak activity varied from one sample of gastric juice to another it was thought due to the presence of saliva or to autodigestion of the gastric juice Thermolability experiments failed to identify the single binding peak of human saliva with either of the vitamin B_1-binding peaks of gastric juice When pepsin was inacti vated by exposure to pH 10 shortly after secretion and before electrophoresis of gastric juice only 1 vitamin B_1 binding peak was found This corresponded with the slower moving peak containing the more thermolabile nondialyzable sub stance It was slowly destroyed by pepsin by diffusion it had a molecular weight of 70 000 The more rapidly migrat ing anodic protein peak was shown to increase when pepsin was not inactivated Only the slow moving peak possessed clinical intrinsic factor activity when administered with a test dose of radioactive vitamin B_1 in patients with perni cious anemia

The author concludes that the slower moving thermola bile vitamin B_1 binding component of human gastric juice is identical with the vitamin B_1 binding mucoprotein iso lated from hog stomach With the evidence of others this supports the view that intrinsic factor and vitamin B_1 binding principle are identical and that assay of intrinsic factor by determining vitamin B_1-binding power of prep arations in which autodigestion has been avoided may be a justifiable procedure

Effect of Transfusions of Erythrocytes on Untreated Per nicious Anemia In 1946 Davidson Murphy Watson and Castle reported the effects of massive transfusions of whole

blood and packed erythrocytes given to 5 patients with pernicious anemia in relapse They stated Following the blood transfusions but prior to liver extract therapy the bone marrow megaloblasts characteristic of pernicious anemia disappeared This statement is open to two interpretations (1) Multiple blood transfusions produce a change in erythrocyte precursors in marrow of patients with pernicious anemia in relapse similar to that after specific therapy with vitamin B_1 or liver extract (2) If the term normoblast is synonymous with late megaloblast (type III and IV) disappearance of megaloblasts would mean that most immature cells have disappeared while the remaining more mature erythrocyte precursors 'normoblasts may still show morphologic evidence of specific deficiency

HEMATOLOGIC CHANGES AFTER ADMINISTRATION OF RED CELLS OR PLASMA

P en	T pe T f ion	% Nucl. R B C. By Stages				M E R io	H t	Hgb. (Gm)	R B C (M / lion)	Absol. Retics
		I	II	III	IV					
							%	%	cu mm	cu mm
Case #1 H R										
7 D y Bef e Tra f o		10	17	65	8	1 4/1	20	6 8	1 6	1400
3 D y Aft T n f on	U ash d ed ll	3	14	65	18	3/1	47	14 7	4 3	4300
Case #2 J T										
7 D y Bef e T fu		9	6	55	30	9/1	10	3 8		16100
D Aft T f	Washed red ll	3	4	61	32	1 6/1	46	14 1	4 9	4900
C se #3 J M										
7 D y Bef T f			9	67	2?	2 2/1	28	8 7	1 7	1 000
8 D ys Afte T fu	W ist d d cell	0 5	4	54	41 5	5 2/1	51	15 8	4 2	0
C se #4 B B										
5 D ys B f e T fu		3	8	7	17	1 5/1	16	4 0	1 2	1600
8 D y Aft T f	Fresh froz l		11	9	8	2 3/1	14	4 3	1 1	4200

James D Mason, Jr and Byrd S Leavell[4] (Univ of Virginia Hosp) report a similar study of 4 patients with pernicious anemia who had not received previous therapy with vitamin B_1 folic acid or liver extract (table) No significant changes were noted in 1 patient who received a transfu

(4) Blood 11 632-640 J ly 1956

sion of 250 cc plasma Following erythrocyte transfusions to produce a normal hematocrit in 3 patients bone marrows showed reduction in early megaloblasts (stages I and II) to less than 50% of pretransfusion levels in 2 patients and to 63% in the other The myeloid erythroid ratio of marrows increased and the absolute reticulocyte count decreased There was no change in the peripheral leukocyte and platelet counts or in the patients clinical condition After therapy with vitamin B_1 when hematocrits were normal bone marrows became normoblastic a small but definite reticulocytosis occurred leukocyte and platelet counts returned to normal and the patients were subjectively improved

In these 3 patients with untreated pernicious anemia multiple transfusions of packed erythrocytes diminished erythropoiesis but did not basically alter the manifes ations of the deficiency state as exhibited by elements of bone marrow and peripheral blood Interpretation of posttransfusion marrows as megaloblastic was supported by the marked morphologic changes in marrow and reticulocytes that followed administration of vitamin B_{12}

► [As pointed out by the authors the use of the term megaloblast by Davidson *et al* was ambiguous However their results were actually in conformity with those of the present authors to whom indebtedness is due for this clarification of terminology Multiple transfusions in pernicious anemia thus seem to remove the secondary effect of anemia on the bone marrow without abolishing the effect of the vitamin B deficiency —Ed]

Subacute Combined Degeneration of Spinal Cord Current Concepts of Disease Process Value of Serum Vitamin B_1 Determinations in Clarifying Some Common Clinical Problems are delineated by Maurice Victor and Arnold A Lear[5] (Boston) with 9 case reports Pernicious anemia is a conditioned nutritional deficiency in which owing to lack of intrinsic factor dietary vitamin B_1 (extrinsic factor) is not absorbed and therefore is not available to perform its essential role in hemopoiesis and maintenance of integrity of the nervous system Folic acid may control the anemia but it is not the intrinsic factor and does not prevent development or arrest progression of neurologic disease in pernicious anemia In fact it may accelerate development of nervous system lesions Deleterious action of folic acid on subacute combined degeneration may be due to a mass action effect accelerating absolute vitamin B_1 depletion to altered

(5) Am J Med 20 896 911 Jun 1956

kinetics of vitamin B_{12} utilization or storage or simply to creation of vitamin imbalance by treating only part of the existing deficiency state

Subacute combined degeneration of the spinal cord still poses many clinical problems Difficulties arise from lack of correlation between the degree of anemia and severity of the degeneration from progression of neurologic disease despite normal hemopoiesis and in differential diagnosis Standard clinical and laboratory methods have obvious shortcomings Estimation of gastric acidity is of limited value—but if acid is present diagnosis of subacute combined degeneration is unlikely Blood and bone marrow studies are helpful but only when results are abnormal Therapeutic trial of vitamin B_{12} may be used but this often means that therapy must be continued indefinitely and that diagnosis may remain in doubt unless additional studies are undertaken

In puzzling cases when anemia is mild or absent or has been corrected by folic acid the serum vitamin B_1 level may be of critical importance This can be measured by a microbiologic technic employing algal flagellate Euglena gracilus Beside excluding various macrocytic anemias vitamin B_1 assay may distinguish cord disease of pernicious anemia from that of other causes In the former vitamin B_1 content is consistently low (below 85 μμ/ml) provided the patient has received no liver or vitamin B_1 injections A normal serum vitamin B_1 (*292 856* μμg/ml) in a patient with posterior and lateral column disease especially if no free acid is present provides convincing evidence that the neurologic disorder is not associated with pernicious anemia

Three patients who were anemic had inadequate blood examinations when first seen and pernicious anemia was not diagnosed Since damage to the nervous system represents a more harmful aspect of this disease than anemia thorough scrutiny of the blood is important in patients presenting neurologic symptoms When peripheral blood is grossly normal and neurologic signs predominate more subtle blood changes such as mild macrocytosis and presence of large and multilobed polymorphonuclear granulocytes in blood and marrow should be sought In these cases the necessity of proper and continued treatment of pernicious anemia was

not fully appreciated In 2 parenteral liver therapy was abandoned and oral vitamins substituted whereas in 2 others oral vitamins were given from the start The practice of prescribing oral multiple vitamin preparations for patients with anemia more specifically of administering folic acid in the presence of vitamin B_{12} deficiency cannot be too strongly condemned Although this has been well substantiated and publicized within 2 years the authors encountered 6 such cases in which despite hematologic remissions neurologic signs developed which were largely irreversible

Erythrokinetics in Pernicious Anemia Clement A Finch Daniel H Coleman Arno G Motulsky Dennis M Donohue and Robert H Reiff[6] (Univ of Washington) describe the quantitative aspects of red cell production in pernicious anemia in relapse and during response to vitamin B_{12} In pernicious anemia the bone marrow is ineffective in producing viable red cells

In untreated pernicious anemia erythroid tissue in the marrow is increased as is the erythroid/myeloid (E/M) cell ratio Inspection of marrow smears indicates adequate amounts of hemoglobin in the cytoplasm of the nucleated red cells Less radioiron is incorporated into hemoglobin than in normal subjects and this iron appears in circulating red cells at a normal rate Yet the E/M ratio plasma iron turnover and fecal urobilinogen indicate a greatly increased erythroid marrow activity Plasma iron turnover reflects hemoglobin or red cell production and is unaffected by red cell breakdown In untreated pernicious anemia it is increased beyond the amount which could be going into turnover of circulating red cells as judged from low reticulocyte counts and red cell radioiron utilization and from red cell survival studies Thus plasma iron turnover is related to total erythropoietic activity but not to *effective* red cell delivery to the circulation It reverts to subnormal levels when erythropoiesis is arrested by transfusions

Composite data in untreated pernicious anemia indicate a total red cell production of three times normal but an effective production of no more than normal Because of the short red cell survival (25 75 days) in the circulation there is appreciable anemia reaching equilibrium at about 15%

(6) Blood 11 807 820 September 1956

hematocrit with an average red cell destruction rate of three times normal Normal cells survive normally in the patient s circulation although De Gowin s precise studies suggest a mild hemolysis until normal vitamin B_{12} metabolism is achieved Most studies indicate faulty cell construction as

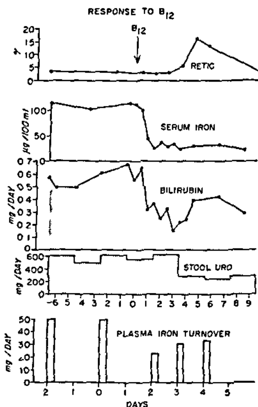


Fig 68 (Courtesy of Finch C A et al Blood 11 807 820 September 1956

the cause of the hemolysis In vivo counting over sacrum sternum and liver and direct counting of blood indicate sustained levels of radioiron in marrow and liver with only a small portion appearing in the circulating red cells Consequently it is assumed that much radioiron labeled red cell destruction occurs in the marrow

The relatively early disappearance of cytoplasmic reticulum compared to nuclear maturity (asynchrony) results in

partial disappearance of the reticulocyte stage of red cell de velopment Therefore it is obvious that the reticulocyte count provides an erroneously low figure of the rate of red cell production The erythroid hyperplasia in pernicious ane mia results from the anemic stimulus since it disappears when the hematocrit returns to normal after transfusions [See article by Mason and Leavell this YEAR BOOK page 257 —Ed] The patient with pernicious anemia cannot in crease his effective blood production above normal despite a severe degree of anemia Due to the deficiency of vitamin

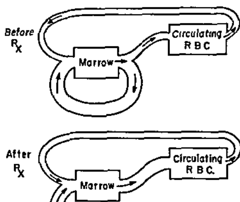


Fig 69 (C rte y f F h C A t l Bl d 11 807-820 S ptemb 1956)

B_{12} even total red cell production falls short of that seen in many hemolytic anemias

The marrow changes rapidly following treatment with vitamin B_{12} from megaloblastic to normoblastic marrow Before the reticulocyte response the normoblasts become reticulated and the marrow reticulocyte pool increases Co incidentally plasma iron and bilirubin fall within 24 28 hours of therapy total plasma iron turnover remains the same or decreases and fecal urobilinogen decreases (Fig 68) These abrupt changes indicate that ineffective eryth ropoiesis with associated hemolysis presumably in the bone marrow is converted to effective red cell production Before therapy 40% of the increased fecal urobilinogen is not derived from the breakdown of circulating red cells With therapy this excessive red cell destruction stops and the iron previ

ously circulating in the plasma between marrow and storage tissues is now locked in maturing red cells (Fig 69) Plasma iron turnover remains the same or decreases indicating that total erythropoiesis is not increased by the therapy

Subsequently erythroid cells no longer mature synchronously in the marrow thus increasing the marrow reticulocytes which then appear in the peripheral blood Early reticulocytes have large amounts of reticulum and may be assumed to remain longer in the blood These two factors lead to an accumulation of reticulocytes of about eight times normal during early remission The average reticulocyte count over 3 weeks however is only three times normal and reflects fairly accurately the rate of blood production

Direct Action of Folic Acid Folinic Acid and Vitamin B_{12} on Megaloblasts in Vivo was studied by P W G Tasker[7] (Inst for Med Res Kuala Lumpur Malaya) in patients with severe megaloblastic anemia of nutritional deficiency or pregnancy Technic employed was similar to that of Horrigan

Marrow was obtained by needle biopsy from the left iliac crest Test substance usually dissolved in 1 ml normal saline was instilled into a needle left in situ After 48 hours biopsy was repeated within 1 cm of the same site with control biopsy from the opposite iliac crest Differential counts (500 cells) on all 3 marrow smears were compared and fell into 3 patterns (1) same proportion of megaloblasts in each smear indicating that substance was inactive or given in insufficient quantity (2) in 48 hour films significant reversion to normoblasts equal at test and control sites indicating general activity of instilled substance and (3) in 48 hour film from test site significant reversion compared with that in initial or control smear indicating direct local effect on megaloblasts

In 22 patients vitamin B_{12} was given at 3 dose levels (0 1 0 5 and 1 μg) Ten received folinic acid 0 5 mg Folic acid was administered in 3 different doses (0 5 1 and 2 mg) to 21 patients in some instances folic acid was dissolved in normal neutralized gastric juice or homologous serum

In vivo folinic acid readily converted megaloblastic marrow by local effect and vitamin B_{12} also had direct local action in some patients in whom deficiency of this vitamin

(7) Brit J Haemat 05 209 Ap 1 1956

could be presumed from subsequent response to treatment There was no evidence that folic acid acted locally Metabolic studies in animals and with bacteria have demonstrated that folic acid is probably converted into folinic acid before exerting a metabolic effect The present study affords evidence in man that folic acid must be converted to folinic acid or a like substance before acting on megaloblasts This confirms some of the contradictory observations of others made on megaloblastic marrow in vitro As here in vivo Reisner and Swan found that gastric juice in vitro did not potentiate the local action of vitamin B_1 However both in vivo and in vitro technics are difficult

Treatment of Megaloblastic Anemia of Pregnancy and Puerperium with Vitamin B_1 was assayed in 10 cases by E B Adams[8] (Univ of Natal) Bone marrow studies showed giant metamyelocytes in all in 6 there were megaloblasts of Ehrlich and cells of intermediate type 4 showed intermediate cells without megaloblasts Bone marrow was reported as megaloblastic if it contained true megaloblasts or intermediate cells and giant metamyelocytes

Early reports from temperate climates indicated that treatment of megaloblastic anemia of pregnancy and the puerperium with vitamin B_1 was usually ineffective In warmer climates response to vitamin B_1 in small amounts was often satisfactory Such differences support the views of Thompson and Ungley (1951) and others that there are several varieties of the condition

Vitamin B_{12} was administered intramuscularly in doses from 100 µg in one injection to 1 400 µg in daily injections of 100 µg Of 7 patients treated after delivery response was good in 6 moderate in 1 Results were as good in 3 who received only 100 µg as in 4 who received much higher doses Average daily hemoglobin rise was 0 16 Gm /100 ml Better results however were usually obtained with folic acid Poor results followed treatment with vitamin B_{12} in all 3 patients seen during pregnancy

In Africa bone marrow differs from that described in megaloblastic anemia seen in temperate climates Giant metamyelocytes are always present but erythropoiesis may be megaloblastic or intermediate There seem to be several varieties of megaloblastic anemia associated with pregnancy

(8) B M J 2 398-400 Ag 18 1956

because of these differences in bone marrow and in response to treatment Despite this cases reported from many parts of the world have much in common They tend to occur in the last trimester or puerperium sometimes onset is rapid, peripheral blood picture is inconstant spontaneous remission may follow delivery dietary deficiencies do not appear the only cause though diets are often poor The common factor may be development of resistance to hemopoietic substances during pregnancy, as Badenoch and his colleagues have suggested rather than absolute deficiencies

► [The results of this study are not very meaningful because of the unphysiologically large doses of vitamin B_{12} employed Failure to respond during pregnancy is not observed with folic acid therapy so that perhaps the postulated inhibition is with respect to the utilization of vitamin B_{12} —Ed]

HYPOCHROMIC ANEMIAS

Iron Metabolism Review with Special Consideration of Iron Requirements during Normal Infancy is presented by Phillip Sturgeon[9] (Los Angeles Children s Hosp) The infant has no route or organ for physiologic excretion of iron *Clinically insignificant* quantities are lost through the skin and gastrointestinal tract Balance studies indicate that at least some infants may have *greater capacity to* absorb iron than adults (whose assimilation does not exceed 10% of iron ingested) The intestinal mucosa tends to act as a barrier to the rapid entrance of iron into the circulation (mucosal block)

Iron in serum is transported bound to a serum *globulin* (siderophilin) present in a two to threefold excess of concentration of iron in the serum (this represents serum iron binding capacity) Relative to adults many normal infants have a reduced concentration of serum iron and increased iron binding capacity Similar changes are seen in iron deficiency states Storage iron is found primarily in the liver and spleen in two chemical forms ferritin detectable only by chemical means and hemosiderin which is visible microscopically and takes iron stains Hemosiderin in bone marrow is reduced in iron deficiency states It is not found in the bone marrow of normal infants

(9) Pediatrics 18 267 298 Aug t 1956

The time required for assimilation of iron including met abolic transport across the intestinal mucosa through the serum iron pool into bone marrow and out into circulating erythrocytes is short as little as 4 hours Most iron metabo lized internally comes from the daily breakdown of hemoglo bin and to a less extent from other iron compounds such as myoglobin cytochrome and ferritin Dietary iron assimilated constitutes only a small percentage of daily total iron turn

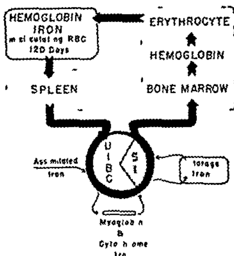


Fig. 70 —I n kinet s Central c rcular wide black line ep esents elati e amou t of ron th t ente s and leaves rculation d ly (on turnover) a ows to d f om va iou r rounding compartm is rep e t relat e mount w thd awn and con tributed daily by ea h *UIBC* reps sents unsatu ated ron b nd g cap ty *SI* serum iron Sum of the two alues eq ls erum total ron b d g cap city (Courtesy f Stu g on P Pediatrics 18 67 298 Augu t 1956)

over (Fig 70) Since studies of iron turnover rates have not been made on infants the magnitude and significance of the factor of rapid growth is not known

The physiologic anemia of late infancy is associated with evidence of depletion of iron in various iron compartments hemoglobin serum iron iron binding capacity and iron stores

Although it is not possible to determine precisely the rel ative importance of various factors influencing the ultimate state of iron nutrition of an infant the following summary of

iron requirements during infancy represents inferences drawn from facts cited by many investigators Among endogenous factors concentration of hemoglobin and blood volume at birth are of great significance Within the normal range of hemoglobin concentration and blood volume infants of the same weight may differ by as much as a factor of 2 in total hemoglobin iron Differences in rate of growth of infants of the same weight and having identical amounts of iron may necessitate as much as a 66% increase in iron requirement of faster growing infants Two newborn infants otherwise alike may differ in the amount of storage iron in the liver and spleen in the technic employed in clamping the umbilical cord and in the relative rate of increase in total *myoglobin mass Each of these causes a slight but sig*nificant alteration in iron requirement during infancy

The range in efficiencies of normal infants gastrointestinal tracts to assimilate iron from natural foods remains to be determined The limits of capacity to compensate for adversity in one or several endogenous factors are greatly exceeded in the full term infant who though receiving a diet containing physiologic amounts of iron develops iron deficiency anemia It is also exceeded in most premature infants irrespective of diet This capacity is apparently reached or slightly exceeded in the infant who develops the physiologic anemia of late infancy

The quantity of iron provided by infants diets varies widely *on milk alone as little as 0 14 mg /day on diets with* iron enriched foods 6 8 mg /day The contribution of diet *to total infant iron nutrition becomes increasingly* important in the average infant after its first year approximately 50% of an infant s total iron is derived from diet by age 18 months In general iron requirements/kilogram body weight in the normal adult may be regarded in terms of a single value that is relatively uninfluenced by slight individual physiologic differences During infancy the average iron requirement/kilogram body weight greatly exceeds that of the adult Besides a normal infant s need for dietary iron may exceed *that of another by as much as 300%*

*Recent data on blood volume and concentration of hemo*globin of the newborn infant suggest reduction in estimates of total iron present at birth A mean value of 200 mg with a

relatively wide range of 120 320 mg for a 3 kg infant is consistent with these data and with total iron content of still born fetuses over 3 kg Calculations show that infants with smaller quantities of iron at birth and relatively rapid growth must assimilate iron at three times the rate of other normal infants

Preliminary studies on the prophylactic use of intramuscular iron indicate that many symptoms of iron deficiency in normal infancy can be altered A statistically significant higher mean concentration of hemoglobin (0 7 Gm /100 ml) was achieved Infants so treated with hemoglobin values under 11 Gm /100 ml were not observed whereas 20% of normal infants at age 1 year had hemoglobin levels of 9 4 11 Gm Highly significant reductions in total iron binding capacity serum copper and free erythrocyte protoporphyrin were achieved Increases in concentration of serum iron and mean erythrocyte hemoglobin concentration were also significant Except for skin staining parenteral iron caused no reactions Iron requirement for the first year of life was given in 3 injections of 1 2 ml without difficulty

Hypochromic Microcytic Anemia of Infancy Iron Depletion as Factor is discussed by Hugh W Josephs[1] (Johns Hopkins Univ) using recently revised figures as a basis for calculations applied to specific infants for whom necessary data are available

The four simple calculations used are (1) iron with which the infant is born (2) iron retained from food (3) iron being used by the tissues and therefore unavailable for hemoglobin and (4) iron combined with total mass of hemoglobin With these figures it is possible to estimate the iron still potentially available for use (reserves or stores) Depletion exists when the difference between the sum of the first pair and of the latter pair has reached about zero

Depletion is due to gain in weight and maximum possible use of iron Therefore it is a normal result of growth and need not be associated with anemia When depletion has occurred the organism becomes dependent on current absorption of iron This is ordinarily sufficient even with a diet of milk alone to maintain an adequate concentration of hemoglobin after age about 8 10 months Severe anemia due to de

(1) P d t 18 959 978 Dec mbe 1956

pletion alone is practically confined to premature babies whose relative gain in weight is rapid Severe anemia in other than premature infants results from se eral factors by which iron becomes unavailable or is actually diverted from hemoglobin to storage Response to iron medication is considerably better in infants with depletion than in those in whom some factor is present that interferes with iron use and is not corrected by giving iron

Dependence on current absorption whether due to depletion or nonavailability introduces a certain precariousness apparently characteristic of this age The organism gets along from day to day if nothing happens but may not be able to meet an emergency such as rapid gain in weight or necessary repair of damage done by severe infection If iron deficiency is considered the cause of anemia deficiency may be regarded as due to several factors of which depletion is only one

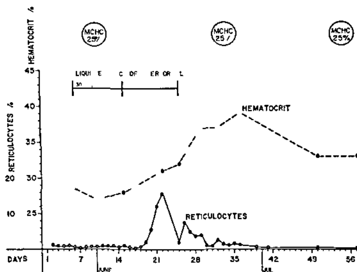
Hypochromic Anemia with Hyperferricemia Responding to Oral Crude Liver Extract Daniel L Horrigan Richard M Whittington Russell Weisman Jr and John W Harris[2] (Cleveland) observed 2 men 38 and 41 with an anemia refractory to therapy with iron vitamin B_{12} folacin and leucovorin but responding maximally to oral administration of liquid liver extract In both the peripheral blood showed erythrocytic anisocytosis poikilocytosis and anisochromia The calculated mean corpuscular hemoglobin concentrations were consistently low whereas the mean corpuscular volumes varied between microcytosis and normocytosis The bone marrow showed erythroid hyperplasia with erythroblastic maturation arrest Abnormal erythroid maturation similar to that seen in the marrow of patients with untreated pernicious anemia was not apparent Serum iron concentrations were elevated with increased saturation of the total serum iron binding capacity In each instance the anemia was of long duration and continuing study failed to reveal an adequate explanation for its development and persistence

Although free hydrochloric acid was present in the fasting gastric contents of 1 patient a histamine fast achlorhydria was demonstrated repeatedly in the other

In the first patient prompt reticulocyte response occurred

(2) Am. J Med 22 99 106 Ja ary 1957

with a peak of 25% on the 9th day of therapy on 30 cc liquid liver extract USP (Valentine®) Erythrocytic regeneration was rapid with a rise in hematocrit from 21 to 42% in 7 weeks With this response the mean corpuscular hemoglobin concentration rose from 25 to 30% Subjective improvement also was prompt About 6 months after cessation of therapy hematologic relapse occurred the hematocrit fell to 30% and the mean corpuscular hemoglobin concentration to 25% In



F g 71—G aph h w g f l f po to l qu d h ext t USP (Cou t y f H g D L t l Am J M d. 2 99 106 J n ry 1957)

later trials the patient failed to respond to 30 cc of the crude extract given in a single daily dose for 10 days (Fig 71) A suboptimal response occurred with 45 cc given in 3 divided doses daily for 10 days

These patients present a unique type of nutritional anemia responding to a factor present in oral crude liver extract which previously has not been recognized as essential in human erythropoiesis The combination of hypochromia of erythrocytes erythroid hyperplasia with decrease in numbers of mature normoblasts in bone marrow and elevated

serum iron levels with increased saturation of iron binding protein and hemosiderin deposition in tissues suggests a failure of iron utilization in the synthesis of hemoglobin Iron not used is deposited in tissues as hemosiderin

Pyridoxine deficiency in animals provides a very similar blood picture The authors recently reported on a man with hypochromic anemia that responded only to pyridoxine The clinical similarities to these cases were striking the principal difference being failure to respond to liquid liver extract U S P (Valentine®) in oral doses as large as 120 cc daily Response to pyridoxine in the presently reported cases has not yet been tested Active fractions obtained from the crude extract of liver have not contained pyridoxine by chromatographic and spectrophotometric analysis

► [Similar patients in small numbers are becoming recognized when instances of hypochromic anemia with high serum iron are investigated —Ed]

OTHER ANEMIAS

Studies on Anemia of Disseminated Malignant Neoplastic Disease II Study of Life Span of Erythrocyte It has been demonstrated previously that the life span of erythrocytes from normal donors is shortened when transfused into patients with leukemia lymphoblastoma and various disseminated carcinomas In addition direct Cr^{51} labeling of red cells of patients with these conditions discloses an intrinsic shortening of the life span of the patient s own red cells These observations suggest a humoral factor in cancer patients which destroys erythrocytes

George A Hyman Alfred Gellhorn and Jane L Harvey[3] (New York) report experiments to determine whether there is also a defect in erythrocytes of cancer patients which increases their susceptibility to destruction Blood from 23 patients hospitalized with histologically proved cancer was studied Transfusion of whole blood from 15 patients to normal subjects was made in 6 instances with Cr^{51} and Ashby labeling simultaneously The normal life span of 120 days was achieved in 3 in which life span studies were carried

(3) Blood 11 618 630 July 1956

out as completely as possible Similar results were suggested by less complete curves obtained in 9 studies when Cr^{51} or Ashby technic was used alone However frequently the dis appearance rate of patients erythrocytes when transfused to a healthy recipient was biphasic the early part of the curve was relatively steep followed by a change in slope with a more gradual decline extending to a normal survival In con trol studies whole blood from volunteers labeled with Cr^{51} or identified by the Ashby method was transfused into other volunteers a 120 day red cell life span was attained in some and suggested by incomplete curves in others

Transfusion of whole blood from healthy volunteers to patients employed Cr^{51} labeling of normal cells in 17 studies Considerable shortening of the life span of these red cells was noted in 7 when compared to other curves but this was not apparent if only the 50% cell survival was used because of a late phase of accelerated destruction Slope of 6 curves sug gested a normal life span

These studies seem to show absence of an intrinsic defect in erythrocytes of patients with neoplastic disease and favor the presence of a hemolytic plasma factor in pathogenesis of anemia of cancer The cancer patient s erythrocytes may be coated with a hemolytic factor which leads to their initially more rapid destruction in a normal environment as when the cells were in the patient s circulation With time how ever because of either dilution in the normal recipient s plasma or failure of its renewal the hemolytic factor fails to be effective and the patient s erythrocytes are then destroyed at a normal rate This speculative interpretation leads to the conclusion that the hemolytic factor is humoral and that its actions on red blood cell survival are reversible

Studies of Anemia and Iron Metabolism in Cancer by Aaron Miller Robert B Chodos Charles P Emerson and Joseph F Ross[4] (Boston) revealed evidence of increased red blood cell destruction based on measurements of fecal uro bilinogen excretion in 6 of 13 patients with malignant neo plasms Increased red cell destruction was also found in 7 of 12 patients by red cell survival studies (Fig 72)

Rate of red cell production as measured by radioiron and red cell survival studies was normal or increased in 29 pa tients but usually failed to compensate for the increased he

(4) J Cl I t 35 1248 1 6 N vembe 1956

molysis with anemia resulting Thus a functional inadequacy of erythropoiesis in the face of a red cell deficit may be considered the fundamental mechanism of anemia in neoplastic disease Anemia was solely attributable to deficient red cell production in 9 patients 4 of whom were totally or nearly free from marrow metastases

Hypoferremia associated with normal quantities of storage iron was a common finding in patients with cancer the

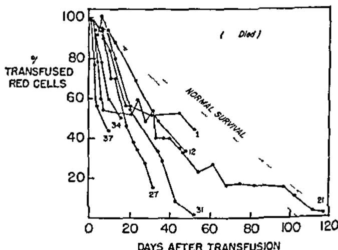


Fig 72 — Increased destruction of normal transfused red cells in 7 patients. (Courtesy of Miller A et al J Clin Invest. 35 1248 126 November 1956)

concentraton of serum iron becoming progressively lower with dissemination of the tumor Hypoferremia was usually but not invariably accompanied by anemia The depression of serum iron levels in the presence of normal or slightly increased quantities of storage iron in cancer has its analogy in acute and chronic infections but the mechanism responsible for the phenomenon is not understood

The half disappearance time (T½) of injected Fe^{59} was abnormally short in two thirds of the patients but this is probably due to the low serum iron level and not to rapid

erythropoiesis External monitoring showed normal patterns for Fe^{59} in 5 patients 2 of whom were anemic In 1 patient with extensive metastases of the lumbosacral spine Fe^{59} failed to concentrate there and in another with signs of increased red cell destruction the high early Fe^{59} uptake over the spleen suggested that it was forming red cells actively

The concept of bone marrow replacement as a common cause of anemia is untenable even when decreased red cell production can be demonstrated It is possible that inadequacy of marrow activity in cancer whether relative or absolute merely reflects an alteration in the homeostatic mechanism which determines the level of hemoglobin concentration or red cell mass in the tumor host

Anemia in Hypopituitarism Treatment with Testosterone and Cortisone Anemia is well recognized as an accompaniment of hypopituitarism but the results of therapy have not been well recorded H B W Greig J Metz and L Sunn[5] (Johannesburg) report a case of hypopituitarism and anemia which responded to hormone therapy alone

Man 29 for 6 years had progressive narrowing of visual fields double vision weakness and apathy loss of facial axillary limb and pubic hair and loss of libido Skull x ray showed an enlarged sella turcica A chromophobe adenoma was removed and he was given postoperative radiation therapy Three months later he had classic signs and symptoms of hypopituitarism Before surgery hematologic studies showed hemoglobin 12 5 gm /100 ml and hematocrit 34% (normochromic anemia) Gastric analysis showed high normal amounts of hydrochloric acid Three months after surgery hemoglobin was 9 6 Gm and red cells 3 500 000 (marked normochromic anemia) Aspiration of sternal bone marrow revealed mild depression of both myeloid and erythroid series Blood volume by the Evans blue dye method revealed low total volume and low red cell volume

Within 2 weeks of the start of testosterone propionate 25 mg 3 times weekly the hemoglobin and red cell count had risen to preoperative levels and a repeat sternal marrow aspiration showed a significant increase in erythroid elements When 25 mg cortisone daily was added to the testosterone treatment the hemoglobin became normal as well as the leukocyte and differential count Weakness and apathy disappeared body and facial hair had grown again and the patient was shaving daily

The bone marrow and the changes after therapy suggest that an increase in erythropoietic activity caused the increase in erythroid elements in the peripheral blood The absolute neutropenia and relative lymphocytosis during the time of

(5) South Af J Lab & Cl M 2 25 61 M b 1956

molysis with anemia resulting Thus a functional inadequacy of erythropoiesis in the face of a red cell deficit may be considered the fundamental mechanism of anemia in neoplastic disease Anemia was solely attributable to deficient red cell production in 9 patients 4 of whom were totally or nearly free from marrow metastases

Hypoferremia associated with normal quantities of storage iron was a common finding in patients with cancer the

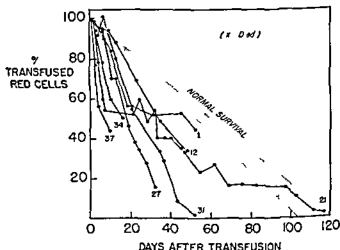


Fig 72—Increased destruction of normal transfused red cells in 7 patients. (Courtesy of Miller A et al J Clin Invest. 35 1248-1262 November 1956)

concentraton of serum iron becoming progressively lower with dissemination of the tumor Hypoferremia was usually but not invariably accompanied by anemia The depression of serum iron levels in the presence of normal or slightly increased quantities of storage iron in cancer has its analogy in acute and chronic infections but the mechanism responsible for the phenomenon is not understood

The half disappearance *time* ($T\frac{1}{2}$) of injected Fe^{59} was abnormally short in two thirds of the patients but this is probably due to the low serum iron level and not to rapid

sponded well to 50 mg cortisone orally daily which was started when the hemoglobin had fallen to 34% and no further transfusion has been necessary An active and apparently normal erythropoiesis was obtained In the peripheral blood a normal hemoglobin level was associated with intermittent reticulocytosis and a sustained erythrocytic hyperchromasia and macrocytosis After almost 1 year of cortisone treatment (50 mg daily) mild azotemia was detected but no other complication attributable to cortisone Reduction of the dose to 25 mg daily corrected the azotemia without the recurrence of severe anemia

That cortisone cured or even corrected the basic disorder is not claimed the study was short termed and no normocytic normochromic erythrocyte status was produced However the therapy proved to be a convenient superior and apparently safe alternative to conventional and obligatory blood transfusions

It cannot be explained why some patients show hematologic improvement from cortisone or ACTH and others do not The initial quantity and qualitative profile of erythroid precursors do not appear to vary significantly from that displayed by some patients who are refractory to cortisone medication

► [In view of the macrocytosis observed here it is of interest to recall that a few years ago Arrowsmith reported that in a similar patient cortisone therapy produced a megaloblastic erythroid marrow and allowed vitamin B therapy to become effective —Ed]

Cobalt in Anemia Anemia associated with kidney diseases in uremia is little influenced by the common antianemic drugs Iron vitamin B_1 folic acid arsenic and liver preparations are generally ineffective Blood transfusions involve the risk of acute or critical aggravation of a latent or manifest pulmonary edema hemolysis or other reactions Profound anemia increases the fatigue nausea and dizziness often present Adequate function in kidneys is said to require hemoglobin levels of 65 70% Cobalt chloride has been reported to produce good results in the anemia of uremia Poul Schleisner[7] (Denmark) re evaluated this treatment in 15 anemic patients with various kinds of kidney disease

The patients first were given iron for several weeks and only if the hemoglobin level remained constant or was fall

(7) A t m d. ca d nav 154 177 185 1956

pituitary insufficiency seen in this patient is characteristic. Testosterone restored the differential leukocyte count to normal but this was not sustained and despite continued testosterone therapy neutropenia and lymphocytosis reappeared The addition of cortisone returned the differential count to normal and it remained so The hematologic remission was complete on hormone therapy alone

Results in this patient bear on hypotheses concerning the influence of endocrine organs on erythropoiesis Crafts observed that combined thyroidectomy and adrenalectomy in the rat reproduced the effects of hypophysectomy on the red blood count hemoglobin and hematocrit and that daily injections of thyroxin and cortisone would prevent the anemia That the pituitary produces a specific erythropoietic hormone has been suggested from time to time and more recently by Contopoulos *et al* It is clear however that from the cases reported and from the present case no pituitary hormone is required to restore the blood picture to normal in man In the present case a high normal gastric free acidity rules out achlorhydria as a cause of the anemia which if so caused would be either hypochromic due to malabsorption of iron or macrocytic due to intrinsic factor failure

► [For further evidence that testosterone propionate has a pharmacologic hemopoietic effect in normal subjects see article by Kennedy and Gilbertsen this YEAR BOOK page 288 —Ed]

Cortisone Therapy in Erythrogenesis Imperfecta Rowland J Calvert and Thomas Robson[6] describe a boy 10 with erythrogenesis imperfecta (Cathie) or pure red cell anemia (Fischer and Hubble) in whom iron and liver therapy was ineffective and whose life was prolonged during a period of 8 years with blood transfusions at approximately 3 month intervals Lowest recorded hemoglobin values (Sahli) were 20% and 14% Reticulocyte counts varied between 0 and 0 3% and leukocyte counts between 6 100 and 16 800 with normal differential counts Platelet counts ranged from 200 000 to 250 000 Myelograms showed very few red cell precursors as the only consistent abnormality Leukopoiesis and megakaryopoiesis were always normal

Cobaltous chloride also failed to produce a hematologic remission The hemoglobin level continued to fall and there was no increase in the reticulocyte count The patient re

(6) Arch Dis Childhood 31 177 181 June 1956

POLYCYTHEMIAS

Plasma Erythropoietic Stimulating Factor in Man Observations on Patients with Polycythemia Vera and Secondary Polycythemia James W Linman Frank H Bethell and Helena K Tascott[8] (Univ of Michigan) found that human nonprotein plasma extracts from patients with polycythemia vera and secondary polycythemia can stimulate erythropoiesis in the normal rat affording direct evidence of a humoral erythropoietic factor in man In the recipient rat this erythropoietic stimulation is manifested by erythrocytosis reticulocytosis and increased marrow erythropoietic activity with no appreciable increase in hemoglobin or hematocrit levels It is suggested that species differences and duration of erythropoietic stimulation may determine increase in red cell mass

The existence of a plasma erythropoietic stimulating factor in patients with secondary polycythemia might be anticipated in view of the effect of hypoxia Its presence in patients with polycythemia vera however is not so readily explained Unless the factor is produced by active myeloid elements considerable significance must attach to its demonstration in patients with polycythemia vera Previous observations on lack of effect of nitrogen mustard or x rays on production of the factor seems to exclude hemopoietic tissue as the site of formation or a regenerative marrow as a prerequisite for its elaboration The phenomenon would therefore appear to be of possible primary importance in pathogenesis of polycythemia vera and not merely a manifestation of heightened erythropoietic activity Though blood leukocyte and platelet observations were not made in the study the constancy of the marrow granulocytic numbers is against any effect on these hemopoietic elements exerted by the plasma factor Although normal human plasma did not possess erythropoietic activity by the bioassay method used the lack of response may be due to its low concentration in normal plasma rather than to its absence

Problem of Leukemia in Polycythemia Vera is unanswered because there has been no large series of patients treated by

(8) J Lab & Clin. Med. 49 113 127 January 1957

ing was cobalt added in the form of 0 2% solution of cobalt chloride 1 dessertspoon 3 times a day corresponding to about 60 mg cobalt chloride or 30 mg of cobalt daily This dose is smaller than that used by most other clinicians Most of the patients were in the chronic or uremic stage of glo merulonephritis pyelonephritis and diabetic nephropathy

Treatment failed in 4 patients One had a tumor of the lung in addition to kidney disease In 1 the blood urea level was 237 mg/100 ml and rose to 372 mg shortly before death In another blood urea level was 301 mg when treatment was begun 22 days before death and another had a level of 126 mg and was not treated until 4 weeks before death Four other patients with blood urea levels between 100 and 200 mg responded to treatment In the other 11 patients hemoglobin increased by 16 68% with an average of 35 4% of the initial value The anemia was initially normochromic Treat ment did not change the color index or the white cells

The most frequent side effect was nausea a difficult symptom to evaluate in patients with uremia In 4 patients it was severe enough to cause discontinuation of the drug Ten of the 16 had no nausea at all One patient became hard of hear ing after 9 months of treatment and a total of about 14 Gm cobalt Neurolabyrinthitis cochlearis was found improved after politzerization but the patient died a few days after cobalt was discontinued

Of 2 patients with atypical macrocytic anemia one may possibly have benefited from cobalt therapy The other who had a toxic anemia had no demonstrable benefit One pa tient with rheumatic fever and anemia did not respond to iron therapy but added cobalt apparently caused the hemo globin to increase from 69 to 89%

In severe uremia cobalt therapy is of doubtful benefit but at blood urea levels between 100 and 200 mg/100 ml co balt therapy may still produce good results It must be ad ministered to selected patients since side effects are too se vere for indiscriminate use It is not intended for prolonged use as a blood tonic Its chief indication is in chronic re fractory anemia in diseases with a bad prognosis primarily renal anemia

further support the rationale of P^{32} as the present method of choice in treating polycythemia

Secondary Polycythemia is a generic term The increased production of erythrocytes and total volume of erythrocytes are related to some other primary disease most frequently those which produce chronic arterial hypoxemia The four main categories reviewed by Charles F Stroebel and Ward S Fowler[1] are polycythemia caused by high altitude and by defects in the cardiopulmonary system and that associated with brain tumors and with endocrinopathies

When normal persons move to high altitudes there is an initial hemoconcentration Rates of turnover of plasma iron increase greatly in the first 12 hours Reticulocyte counts reach a peak in about a week and this is followed in a few days by an increase in total erythrocytic mass When natives of high altitudes descend to lower altitudes the rate of erythropoiesis decreases markedly

Diseases of the heart and lungs such as cyanotic congenital heart disease pulmonary disease with heart failure pulmonary fibrosis severe emphysema and chronic asthma with resulting hypoxemia may produce secondary polycythemia characterized by an increased total erythrocytic mass and increased viscosity of blood These patients rarely have splenomegaly leukocytosis or thrombocytosis Plasma radioiron turnover is increased but not to the magnitude seen with comparable erythrocytic mass in polycythemia vera

Arterial hypoxemia may result from reduction of oxygen tension in inspired air as in high altitudes depression of the minute volume of alveolar ventilation direct or anatomic venous arterial shunts so called functional shunts resulting from venous blood passing through poorly ventilated portions of the lung in which the blood is only partially reoxygenated as well as from alterations in the thickness or area or both of the alveolar capillary membrane that impair the capacity of the lung to transfer oxygen from the alveolar gas to the capillary blood by diffusion Obesity especially in combination with chronic pulmonary disease may limit pulmonary ventilation In these conditions significant secondary polycythemia is usually not seen unless arterial oxygen saturation at rest is less than 85 90%

Patients who have increased intracranial pressure may

(1) M Cl North Am nc 40 1061 1076 J ly 1956.

means other than radiation and follow up has been inade quate S P Masouredis and John H Lawrence[9] (Univ of California) analyzed the clinical and follow up records of 179 patients with polycythemia vera treated with radiophos phorus between 1936 and 1953 Of these 22 developed a leu kemic picture at some time in the clinical course Ideally this problem would best be studied by comparing the inci dence of leukemia in P^{32} treated patients with the incidence in untreated patients but such an analysis is impossible at the present Therefore the treated group was compared with patients seen before radiophosphorus became available

Patients who developed a leukemic type of picture during P^{32} therapy differed before therapy was started from those who did not The leukemic group had higher white cell counts greater incidence of immature white cells in periph eral blood and a significantly greater frequency of the triad high leukocyte count splenomegaly and immature white cells The frequency of circulating myelocytes was signifi cantly greater These findings suggest that there is no sim ple or direct etiologic relation between radiophosphorus ther apy and development of leukemia in patients with polycythe mia vera

The leukemic potential is present before P^3 therapy is instituted Polycythemia vera is a disease which involves all the marrow elements frequently terminating in leukemia osteosclerosis myelofibrosis myeloid metaplasia and other diverse pathologic entities Two patients have previously been reported in whom acute leukemia developed although they had been treated with only venesection

Roentgen ray therapy tends to suppress the findings as sociated with panmyelosis as evidenced by the more marked differences in clinical determinations seen between the leu kemic and nonleukemic groups when patients with x ray therapy are excluded

The median survival was 18 7 years for the nonleukemic group and 11 9 years for the leukemic group whereas me dian survival after P^3 therapy was 13 3 years and 6 7 years respectively

These findings indicate that the tendency to leukemia is evident before P^{32} therapy The superior results obtained with P^3 when compared with other methods of therapy

(9) Am. J M Sc 233 268 274 M r h 1957

► [Phlebotomy in our experience cannot be uniformly advocated for secondary polycythemia with arterial unsaturation In some patients the increased hemoglobin may be required for adequate tissue oxygenation or phlebotomy may produce in congenital heart lesions hypovolemic circulatory failure According to Walter Goodale fullness in the head accompanies plethora and suggests that phlebotomy may be beneficial In any case phlebotomy should be cautious with arrangements for *prompt* reinfusion of blood or an equivalent plasma expander A delay of a day or two between bleedings will allow time for the subjective evaluation by the patient that is the ultimate criterion of benefit

The following articles illustrate some of the conditions referred to as secondary polycythemia —Ed.]

Polycythemia Associated with Disturbed Function of Respiratory Center The determination of the arterial oxygen saturation in polycythemia separates this condition into two groups Patients with polycythemia vera show normal arterial oxygen saturation and have normal ventilatory function with slightly decreased blood CO content Most have a palpable spleen On the other hand secondary polycythemia associated with arterial hypoxemia occurs in high altitude dwellers in chronic lung disease in congenital heart disease and to a lesser degree in certain acquired cardiac conditions Other causes of secondary polycythemia are exposure to certain chemical agents that may change the hemoglobin molecule so that it is no longer capable of carrying oxygen and consequently polycythemia may develop A relatively mild polycythemia is found in some of the endocrine states such as Cushing s syndrome [or may be induced by the administration of androgenic substances or of cobaltous chloride —Ed]

Peter Pare and Louis Lowenstein[2] (McGill Univ) present a case

Man 35 had absolute polycythemia with arterial hypoxemia He had always been nervous and subject to intermittent depressions and obsessive tendencies For 3 years there had been exposure to yellow phosphorus He was moderately overweight had no cardiac or pulmonary disease but suffered from decreased ventilatory function due to a very small tidal air of 265 ml at rest which was consequent to an impaired respiratory centrogenic drive The basic defect in respiratory function was a marked degree of alveolar hypoventilation This was responsible for a moderate degree of hypoxemia (arterial oxygen saturation of 86%) and a retention of carbon dioxide (CO_2 content 59 8 vol % pCO_2 58 mm Hg) The CO excess was compensated by renal retention of base as is evidenced by the normal pH

Hematologic examination showed hemoglobin 19 9 Gm /100 ml

(2) Blood 11 1077 1084 Decembe 1956

also have increased values for hematocrit and hemoglobin However this is due to reduced plasma volume The absolute erythrocytic volume remains normal This 'relative polycythemia is related to chronic dehydration and is not a disease of excessive erythropoiesis True polycythemia is present in patients who have certain subtentorial tumors, notably cerebellar hemangioendotheliomas Control of such tumors improves the polycythemia but the mechanism involved is unknown

Polycythemia is mentioned frequently as a feature of certain endocrinopathies notably Cushing s syndrome Patients often exhibit a mild increase in hemoglobin and erythrocytes and thus are considered polycythemic However they have never been adequately studied for blood volumes and may represent relative polycythemia

The primary differential diagnoses are secondary polycythemia polycythemia vera and relative polycythemia Splenomegaly may occur in both the primary and secondary forms although it is not common in secondary and is never pronounced Leukocytosis and thrombocytosis are not characteristic of secondary polycythemia although associated infections may produce leukocytosis Many patients with polycythemia vera do not have leukocytosis or thrombocytosis Differentiation in many cases rests on studies of arterial oxygen saturation When significant hypoxemia is found the respiratory or circulatory abnormality can be further sought Blood volume studies usually differentiate secondary from relative polycythemia

After the diagnosis of secondary absolute polycythemia is made phlebotomy is indicated for immediate reduction of *the excessive erythrocytic volume This also reduces* the viscosity of blood and improves its flow Definitive therapy of the primary disease is paramount when possible including relief of bronchial spasm and pulmonary infections liquefaction of tenacious bronchial secretions use of digitalis and cardiac operations Persons living at high altitudes should return to low altitudes Obese persons must be given diets so they will lose weight Radiophosphorus is not indicated until phlebotomy and treatment of the primary disease have had time to be effective In the few cases in which radiophosphorus has been used results are not as good as in polycythemia vera

90 3% at rest He was put on an 1 800 caloric diet In 76 days he lost 97 lb vital capacity increased from 2 4 to 3 5 L and hemoglobin and hematocrit fell respectively to 16 5 Gm and 49 5% He abandoned his diet after leaving hospital and did not return for further laboratory studies

CASE 2—Woman 68 was hospitalized in June 1955 because of dyspnea and orthopnea She had marked obesity for 10 years before admission and cyanosis of face and lips or 4 years An episode of congestive heart failure had occurred 3 weeks previously Cyanosis of lips and finger nails with acute dypsnea was observed on admission Height was 5 ft 4 in weight 229 lb and blood pressure 210/104 mm Hg There was less than 1 cm change between maximal inspiration and expiration of chest Edema of lower extremities was 2+

Laboratory tests showed hemoglobin 18 6 Gm hematocrit 60 5% erythrocyte count 6 400 000/cu mm with normal leukocyte distribution except for 2% neutrophilic myelocytes and 2% basophils Platelet count was 150 000/cu mm reticulocyte count normal mean corpuscular volume 101 cu μ and mean corpuscular hemoglobin concentration 31% Bone marrow studies revealed mild normoblastic hyperplasia Routine urinalysis was normal and CO_2 combining power was 37 mEq/L (82 1 vol %) but other serum electrolytes were normal Arterial oxygen saturation at rest was 63% on room air and 100% while patient was breathing 100% oxygen

Patient was put on an 800 calorie diet and hospital observation continued for 70 days Digitalis was discontinued soon after admission Oxygen was required in the first 3 weeks for episodes of dyspnea with marked cyanosis A trial dose of 5 mg morphine sulfate on the 6th hospital day resulted in lapse into stupor with Cheyne Stokes breathing Two phlebotomies were performed in the 2nd week with removal of 1 100 ml of blood No other therapy was used The patients was discharged 8 weeks after admission On weight reduction dyspnea had subsided arterial oxygen saturation on room air increased to 93 5% and polycythemia was gradually reversed (Fig 73) Three months after discharge she felt well and tolerated moderate activity without dyspnea

In this syndrome hematologic changes are limited to erythroid elements with increased number and perhaps size of red blood cells Neither leukocytes nor platelets are raised Diffuse hyperplasia involving the myeloid and megakaryocytic series characteristic of polycythemia vera is not observed in the bone marrow Estimated total blood volume is slightly elevated with markedly increased red cell volume and decreased plasma volume

It appears likely that the sequence of events leading to polycythemia is initiated by a reduction in alveolar ventilation The thoracic cavity is crowded by fat from within and

red cell count 6 400 000 mean corpuscular volume 106 cu μ and mean corpuscular hemoglobin concentration 29% Reticulocytes were less than 1% Total blood volume was 5 780 cc White count was 9 200 with a normal differential Platelets bleeding time clotting time prothrombic activity and the Rumpel Leede test were normal Sternal bone marrow aspiration revealed normal cellularity Fragility of red cells to hypotonic saline was normal In the differential smears a few red cells were seen which seemed slightly larger than normal but no oval well hemoglobinated macrocytes were present. No target cells were found, and the only abnormalities were the presence of a slight increase of reticulum cells and possibly a slight increase of eosinophilic granulocytes

The normally functioning respiratory center is remarkably sensitive to even the slightest increase in blood pCO_2 and responds by initiating a vigorous hyperventilation The diminished response to 5% CO elicited in this patient was identical to that seen in patients with advanced emphysema showing hypoxemia and hypercapnia It is suggested that the primary defect was in the respiratory center which caused alveolar hypoventilation, arterial hypoxemia and in time a secondary form of absolute polycythemia

Polycythemia of Obesity Further Studies of Its Mechanism and Report of Two Additional Cases are presented by Max H Weil and Ananda S Prasad [3] A 5% incidence of polycythemia in a group of 250 obese patients studied in Mexico was previously described An earlier paper reported on 3 patients with polycythemia associated with obesity and the hematologic findings differed from those in polycythemia vera Incidental reference to the presence of obesity in cases of atypical erythremia and observance of unusual plethora in obese persons were made by several authors An analysis of the frequency with which polycythemia occurred in obese persons at the University of Minnesota revealed that polycythemia was 10 times more frequent in the pathologically obese than in the unselected hospital population Since polycythemia of obesity subsides with reversal of obesity it is important to distinguish it from polycythemias which do not respond to such simple therapy

Case 1 —Man 45 complained of shortness of breath ankle edema and nocturia Obesity had been present since early childhood and weight had increased from 230 to 360 lb in the past 3 years Initial hematologic results showed 5 820 000 erythrocytes/cu mm 18 Gm hemoglobin and 58% hematocrit Arterial oxygen saturation was

(3) An Int Med 46 60 67 January 1957

Five years previously she had experienced severe pain in the back and left shoulder region and hematemesis due to liver trouble Later marked varicosities in the lower limbs and dependent edema gradually developed On physical examination the cardiovascular and respiratory systems were normal The abdomen was greatly distended but without ascites A firm nontender liver was palpated 3-4 fingerbreadths below the costal margin, as well as a greatly enlarged spleen Hemogram showed 8 700 000 red cells 16 6 Gm. hemoglobin color index 0 57 hematocrit, 63% mean corpuscular volume 70 cu.μ and mean corpuscular hemoglobin concentration 26% There were 6 400 leukocytes and 500 000 platelets/cu mm Liver function tests showed bilirubin 1.75 mg alkaline phosphatase 26 King Armstrong units prothrombin 25-45% (after vitamin K) bromsulfalein 70% retention

X rays showed normal heart and lungs and esophageal varices A venogram of the inferior vena cava showed coning below the diaphragm. Laparotomy revealed portal hypertension and the portal venogram showed intrahepatic obstruction An area of thickening or calcification was felt on the right side of the inferior vena cava behind the liver Liver biopsy showed only a portion of one portal tract containing a bile duct but liver cells appeared to be normal and there was no evidence of inflammation or fibrosis

After P^{32} had been administered for 5 months and polycythemia was adequately controlled a splenorenal shunt and splenectomy were performed The liver was nodular and moderately enlarged. The spleen revealed histologic changes typical of portal hypertension. Sections from the splenic vein showed several thrombi Two months later there were 5 000 000 red cells 13 12 Gm hemoglobin 4 480 white cells and 265 000 platelets About 14 months after surgery the patient was in excellent health and had no serious symptoms but still had esophageal varices Plasma prothrombin was normal Hemogram was not repeated.

The authors regard the case as an instance of polycythemia vera in a young woman with associated Budd Chiari syndrome involving thrombosis of hepatic veins and inferior vena cava Two other types of hepatic involvement may develop in polycythemia vera Mosse s syndrome or hepatic cirrhosis and hepatomegaly due to chronic hyperemia Today with splenorenal or portocaval anastomosis possible by surgical means the recognition of such complications is no longer only of academic importance

► [Polycythemia vera seems an unlikely basis for the development of the Budd Chiari syndrome in such a young patient because of the rarity of polycythemia vera at this age. Indeed the only hematologic feature suggesting polycythemia vera is the single elevated platelet count. The initially high red cell count reduced below normal by 4 months of P^{32} therapy had again begun to rise from a low of less than 4 000 000/cu. mm. Thus the effect of P^{32} was wearing off when the splenorenal shunt seemingly put a permanent end to the polycythemia. This does not sound like the usual

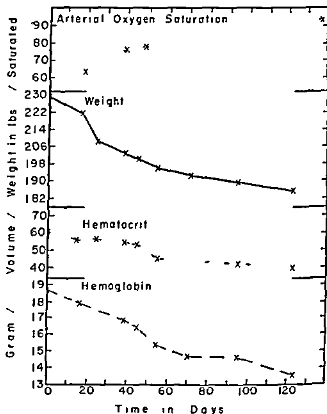


Fig 73—Relationship of hemoglobin hematocrit and arterial oxygen saturation values to weight loss. (Courtesy of W L M. H and Prasad, A. S A n. Int. Med 46 60 67 January 1957)

without and total lung volume is therefore decreased With weight reduction there is a reversal of the syndrome hemoglobin concentration venous hematocrit and CO_2-combining power are brought to near normal values with a corresponding increase in vital capacity and arterial oxygen saturation

Diagnosis and Treatment of Budd Chiari Syndrome in Polycythemia Vera. O FitzGerald P FitzGerald D Cantwell and J A Mehigan[4] (St Vincent s Hosp Dublin) report a case

Woman *22* without family history of polycythemia appeared cyanotic with prominent hepatosplenomegaly on entry to hospital

(4) Brit. M J 2 1343 1345 Dec. 8 1956

Five years previously she had experienced severe pain in the back and left shoulder region and hematemesis due to liver trouble Later marked varicosities in the lower limbs and dependent edema gradually developed On physical examination the cardiovascular and respiratory systems were normal Th abdomen was greatly dis tended but without ascites A firm nontender liver was palpated 3-4 fingerbreadths below the costal margin as well as a greatly enlarged spleen Hemogram showed 8 /00 000 red cells 16 6 Gm hemoglobin color index 0 57 hematocrit 63% mean corpuscular volume 70 cu μ and mean corpuscular hemoglobin concentration 26% There were 6 400 leukocytes and 500 000 platelets/cu mm Liver function tests showed bilirubin 1 75 mg alkaline phosphatase 26 King Arm strong units prothrombin 25-45% (after vitamin K) bromsulfa lein 70% retention

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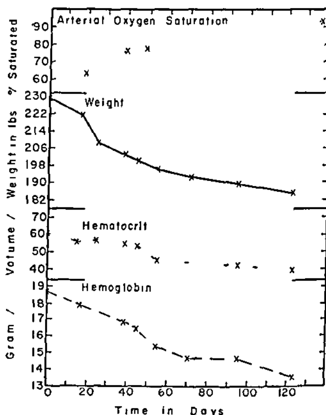


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white cell pattern The platelets appeared normal Measurements of red cell mass in 11 patients before or shortly after testosterone therapy was begun revealed anemia in all A hemopoietic response was evident in 6 The red cell mass increased significantly in all 6 and rose to or above normal in 4 The highest values were after 2 to 4 months of therapy No patient received iron or other hematinics Increase in hemoglobin showed no correlation with tumor response

In some patients red cell and hemoglobin concentrations and red cell mass increased to polycythemic levels Anoxia and cobaltous chloride are the only other agents that will so act Although in male animals and man castration with loss of androgenic activity abolishes the normal sex difference in hemoglobin levels it is now apparent that sufficient androgenic hormone may increase hemoglobin above the normal male levels These results suggest that androgenic hormones may be of value in treatment of refractory anemias

► [Here androgens as do other hormones are shown apparently to function both physiologically and pharmacologically To date with respect to a direct effect on erythropoiesis androgens stand alone among hormones when used as pharmacologic agents Vitamins essential in erythropoiesis are not known to have an enhanced effect in pharmacologic dosage —Ed]

SPLEEN AND BLOOD DISORDERS

Evaluation of Splenic Puncture by the method of Moeschlin as applied in hematologic diagnosis is presented by Jack W Shields and Malcolm M Hargraves[6] Normal splenogram based on 5 000 nucleated cells counted in preparations from 5 control punctures done on each of 4 histologically normal spleens removed during surgery on 52 control splenic aspirates and from the literature is outlined as follows 70% lymphocytes (65% mature 4 9% reticular or immature and 0 1% hemopoietic reticular cells) 25% granulocytes (22 7% segmented 1 5% band 0 6% eosinophils and 0 2% basophils) with practically no cells younger than the metamyelocytes 2 5% monocytes and less than 2 5% endothelioid cells macrophages histiocytes Turk cells plasma cells and pulp cells

Analysis and correlation of splenograms on material aspirated from 60 patients with clinically enlarged spleens in

[6] J Lab & Clin Med 31 440 453 Aug 8 1956

chronic or progressive course of polycythemia vera but does resemble the relief of secondary polycythemia by cardiac surgery for example in closing a right to left shunt in the heart

Unfortunately no measurement of the arterial oxygen saturation was made but the patient had a cyanotic hue which is certainly consistent with arterial oxygen unsaturation In the absence of manifest heart or lung pathology how is this possible? In the first place such lesions as a pulmonary arteriovenous fistula might not have been detected without special effort However what was amply demonstrated was portal hypertension and the presence of esophageal varices In other words the essential vascular potentialities for a flow of blood between the portal vein and the pulmonary veins Such communications have been demonstrated to develop in hepatic cirrhosis and have been shown thus to provide a basis for arterial oxygen unsaturation in such patients by Abelmann *et al* (J Clin Invest 34 919 June 1955) Blackburn (Thorax 11 30 35 March 1956) in connection with a case report ably discusses portal pulmonary vein anastomoses In such vascular connections the direction of flow is necessarily from the high portal pressure to the low pulmonary vein pressure Thus it seems most probable that this cyanotic patient had polycythemia secondary to the entry of unsaturated portal venous blood into the arterial system via the pulmonary veins If so surgical relief of the portal hypertension would diminish the amount of such venous admixture and so might abolish permanently a secondary polycythemia—Ed]

Increased Erythropoiesis Induced by Androgenic Hormone Therapy B J Kennedy and A Sigrid Gilbertsen[5] (Univ of Minnesota) treated 68 patients who had advanced breast cancer with androgenic hormones Stanolone was administered to 37 and testosterone propionate to 31 in dosage of 100 mg intramuscularly 3 times a week

Clinical and laboratory manifestations of flushing and increased erythropoietic activity occurred in 24 patients (35 3%) Duration of therapy was 2 11 consecutive months before maximum erythropoietic effects occurred Subjective clinical manifestations preceded the increased hemoglobin level At the maximum rise in hemoglobin the patient s complexion was plethoric with an appearance similar to that in Cushing s syndrome

In the 24 patients with increased erythropoietic activity the average maximum hemoglobin level reached during therapy was 17 2 Gm whereas the average rise was 4 3 Gm The average increase of hematocrit was 11 2% and accompanied the rise of hemoglobin The red cell counts mirrored the changes of the hemoglobin and hematocrit No alteration was noted in the total white cell or differential count The bone marrow at the time of maximum erythropoietic activity revealed normoblastic hyperplasia with no alteration in

(5) New England J Med 256 719 726 Apr 18 1957

white cell pattern The platelets appeared normal Measurements of red cell mass in 11 patients before or shortly after testosterone therapy was begun revealed anemia in all A hemopoietic response was evident in 6 The red cell mass increased significantly in all 6 and rose to or above normal in 4 The highest values were after 2 to 4 months of therapy No patient received iron or other hematinics Increase in hemoglobin showed no correlation with tumor response

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(6) Proc Staff Meet M yo Cl 31 440-453 Aug 8 1956

dicate that splenic puncture was diagnostic in 15% confirmatory or helpful in 33 3% contributed no diagnostic information in 35% added confusion in 11 7% and was definitely misleading in 5% This evaluation was based on clinicopathologic study of patients followed 1 4 years The majority of cases in which splenic puncture was diagnostic or helpful fall into two groups (1) malignant lesions of the hemopoietic system such as multiple myeloma reticulum cell sarcoma and subleukemic reticuloendotheliosis and (2) myeloid metaplasia and demonstrated absence of cells of group (1) in the spleen Splenic puncture proved most helpful when a paucity of other material was available for laboratory study

Over 90% lymphocytes in the splenogram is not a reliable criterion for diagnosis of lymphocytic lymphoma 11 6% of patients with this percentage of lymphocytes had other conditions whereas one control puncture of a normal spleen showed 95 4% lymphocytes Recognition of atypical or malignant cell types may be diagnostic There was close correlation between myeloid immaturity in peripheral blood smear and myeloid immaturity in the splenic aspirate of myeloid metaplasia making splenic puncture seem unnecessary

Variation in ratio of granulocytes to lymphocytes in control splenic aspirate is such that this ratio has little diagnostic significance Ratio of reticular lymphocytes to mature lymphocytes however seems significant In 20 punctures of 4 histologically normal spleens average ratio was 0 07 with a range of 0 02-0 14 Decrease in relative numbers of reticular lymphocytes seems associated with hemolytic disease while high numbers of these cells are usually found in nonhemolytic conditions A good correlation seems to exist between *myeloid activity of bone marrow and ratio of reticular lymphocytes* to mature lymphocytes in splenic aspirate Of 13 patients with low ratios of reticular lymphocytes to mature lymphocytes 7 had hypoplastic or fibrotic marrows and 4 had hyperplastic marrows Conversely of 9 patients with an elevated ratio of reticular to mature lymphocytes 6 showed hyperplastic marrows and 3 normal cellularity Several patients with clinical hypersplenism showed an abnormally high ratio of reticular to mature lymphocytes suggesting that hypersplenism might be associated with both relative and absolute increases of reticular or immature lymphocytes in the spleen An extremely low ratio was found with myel

ohbrosis associated with myeloid metaplasia of the spleen

Studies on Pathogenesis of Splenic Anemia In a variety of disorders an enlarged spleen is associated with an anemia which cannot be shown to be due to an intrinsic cell defect or an immunologic mechanism The spleen has been implicated in the anemia as a destroyer of red cells or by inhibiting marrow activity E R Giblett A G Motulsky F Casserd B Houghton and C A Finch[7] (Univ of Washington) produced experimental hypersplenism in rats and studied the manner in which this causes anemia

Following the method of Palmer *et al* repeated intraperitoneal injections of the macromolecular inert polymer methylcellulose were given to rats for a 15 week period Comparative measurements of red cell life with Cr^{51} in normal methylcellulose treated and splenectomized animals showed a marked decrease of Cr^{51} labeled red cell survival in the methylcellulose rats Slight but statistically insignificant increased survival beyond normal could be demonstrated in animals whose spleens were removed Excessive red cell destruction occurred in the spleen since Cr^{51} radiation rapidly localized in this organ Size of the spleen could be directly correlated with severity of hemolysis and hemolysis decreased significantly after splenectomy Hemoglobin turnover studies (table) show a remarkable increase in hemo

HEMOGLOBIN TURNOVER IN NORMAL AND METHYLCELLULOSE RATS

Animal	Blood Vol (ml)	Circ. Hgb (mg)	Spleen H (mg)	Total Hgb (mg)	Measured Cr Life (Days)	Hgb produced and destroyed per day (mg.)	Production Rate (times normal)†
M41	19 5	1618	731	2349	1 9	1236	19 8
M1	26	3040	435	34 4	4 5	773	9 1
M20	20 4	2611	435	3046	4 0	60	11 4
M56	14 5	1413	286	1779		659	14 1
M43	1 1	1	3 4	2076	4 3	483	9 8
M57	1 9	1974	258	189	4 8	455	8 8
M47	1 5	2123	236	2359	5 3	445	8 6
M59	15 9	2115	165	2750	5 2	438	8
M10	16 4	1968	165	133	6 3	339	6 3
Average Normal	16 1	250	18	2410	50	5	1

M t methylcellulose rat
†Obtained by comparing hemoglobin produced per day in methylcellulose (corrected to blood volume of 16 1 ml.) with hemoglobin production in normal

ylcellulose were given to rats for a 15 week period (see above)

(7) Blood 11 1118 1130 December 1956

globin turnover in the rats treated with methylcellulose

The combination of marked decrease in red cell life span increase in reticulocytes and hyperplastic red cell marrow indicates increased red cell destruction with compensatory production The anemia is not caused by the methylcellulose alone since rats with spleens previously removed and treated with this substance have normal hemograms Red cells from injected animals survive normally in normal animals but normal injected cells are rapidly taken up by the hypertrophied spleen in treated animals and splenectomy reverses the hemolytic process There is no intrinsic defect in the red cell no depression of marrow and no evidence for splenic hemolysis or for an autoimmune mechanism Affected spleens showed red cell congestion of the pulp and about twice the normal amount of hemoglobin was found per unit spleen mass Quantitative measurements of splenic phagocytosis showed a marked increase of total phagocytic mass but no significant increase of phagocytes per unit of spleen mass

The mechanism of this splenic anemia is thought to be the enlarged pulp compartment with resultant sequestration stasis and cell destruction Methylcellulose induced splenomegaly may be considered an experimental model for the study of the hyperfunctional spleen in human disease

► [Here is excellent evidence confirming the work of Palmer *et al* who showed that the methylcellulose enlarged spleen of the rat is functioning largely if not entirely as a filter in producing hemolytic anemia This view concerning splenic function repeatedly emphasized since 1940 by Ham and his associates has recently been elegantly defined in a variety of human hemolytic anemias by Cr^{51} labeling of red cells and subsequent body surface radioactivity measurements especially by Jandl *et al* (this YEAR BOOK p 242) However the present observations in rats do not mean that hypersplenism is necessarily or perhaps ever a primary specifically splenic process Indeed the fact that splenic enlargement produced by a completely foreign agent such as methylcellulose causes a hemolytic anemia emphasizes the lack of any biologic specificity for so called hypersplenism Today one may postulate simply that the essential property of the spleen in hemolytic anemias is its function as a filter Whether this filter is enlarged nonspecifically by chronic passive congestion (cirrhosis) or by infiltration (lymphoma or Gaucher's disease) or without any such change is merely a more efficient organ for red cell sequestration because of a greater susceptibility of individual (spherocytes) or of aggregated sensitized red cells to be filtered there may result increased red cell destruction and hemolytic anemia Compared to this array of facts convincing evidence for an inhibitory effect of the spleen on erythropoiesis has yet to be disclosed —Ed]

Siderocytes and the Spleen A siderocyte is a red blood cell with one or more granular inclusion bodies which contain

enough ferric iron to give a positive Prussian blue reaction About 50% of the erythroblasts in normal bone marrow contain these granules and it is generally accepted that siderocytes in the peripheral blood are descendants of the sideroblasts in the bone marrow There are few if any siderocytes in the blood of normal persons even in diseases characterized postsplenectomy by many siderocytes they are rare when the spleen is intact The appearance after splenectomy of red cells with iron inclusion bodies has stimulated much speculation regarding the effect of the spleen on this phenomenon

William H Crosby and Naomi R Benjamin[8] (Walter Reed Army Med Center Washington DC) transfused blood containing high concentrations of siderocytes into 4 recipients with spleens and into 2 without spleens In the circulation of the former the siderin granules rapidly disappeared whereas the transfused red cells remained In the latter both granules and red cells remained These experiments demonstrate that the spleen is somehow able to remove the inclusion bodies without destroying the cells

After splenectomy in certain conditions other intra-erythrocytic inclusion bodies may become more numerous—red cell nuclei Howell Jolly bodies malarial plasmodia organisms of bartonellosis Heinz bodies The authors wonder whether a normal function of the spleen is to assist the circulating red cells to rid themselves of any inclusion bodies as it does the siderocyte If true this might be called the pitting function of the spleen

► [A beautiful example of concise clinical investigation!—Ed]

LEUKOCYTOSIS AND LEUKOPENIA

Infantile Genetic Agranulocytosis (Agranulocytosis Infantilis Hereditaria) New Recessive Lethal Disease in Man is described by Rolf Kostmann[9] Onset is during early infancy with fever and skin infections manifested as boils and phlegmons Granulocytes in peripheral blood are completely or almost lacking Bone marrow displays marked retardation

(8) Blood 12 265 170 F brua y 1957
(9) A t p d e 45 309 310 M y 1956

or block in maturation of myelopoietic cells Without treat ment the disease is brief ending in death If infections are treated with antibiotics affected children may survive several months or years Agranulocytosis and pathologic changes in bone marrow remain and death can only be postponed

Fourteen children (boys and girls) in 9 families are reported with detailed clinical and histologic data in 6 Others died before study began Most affected children could be referred to a common pedigree by objective genealogic methods *All belonged to the same geographic isolate inasmuch* as the children were born there or both parents had ancestors there Close consanguinity between parents was established in 5 of the families

Genetic analysis confirms that this disease is caused by a single recessive autosomal gene difference (a simple recessive mutation) The geographic isolate had a population of 9 215 in 1950 Incidence of infantile genetic agranulocytosis among the newborn was estimated at 1 674 or 0 0015 This should correspond to a gene frequency of approximately 4% and heterozygote frequency of about 8% These estimates are uncertain however because of small effective population size

Pathogenetically infantile genetic agranulocytosis is probably caused by primary changes in function of bone marrow Experiments with in vitro cultures of bone marrow cells seem to indicate a primary effect of the mutated gene on certain metabolic pathways possibly of the amino acids

Blood Picture in Rubella Its Place in Diagnosis F K M Hillenbrand[1] made routine white blood cell and differential counts in 443 cases of clinical and 83 of subclinical rubella and compared them with those in 108 cases of measles scarlet fever infectious mononucleosis and rheumatoid arthritis

Initial neutropenia and lymphopenia were seen in less *than* half the rubella cases At later stages lymphocytosis was infrequent and polymorphonuclear leukocytosis almost absent An outstanding feature was regular occurrence of Turk and plasma cells invariably present to the 10th day and usually persisting many months Maximum percentages observed in single specimens were 19 (4th day) 14 (3d day) and 8 (6th day) Monocytes were abundant amounting to 16 18% on

(1) La t 66 68 J ly 14 1956

several occasions Large degenerate lymphocytes often with eccentric nuclei were found at all stages of rubella but usually were a late feature Basophils were sometimes numerous at late stages (to 420/cu mm) A slight initial increase in eosinophils was also observed Metamyelocytes were found in insignificant proportions and were confined mostly to blood from infants Stab cells were only slightly increased

In conjunction with lymph node enlargement routine white blood cell counts are sufficiently characteristic in rubella to permit a confident diagnosis even in subclinical infections Turk and plasma cells alone do not prove the illness to be rubella (these are also present in measles) but diagnosis is practically certain if the blood also shows other characteristic changes of rubella A person without Turk or plasma cells is unlikely to have had rubella

Hematologic Observations in Bacterial Endocarditis Especially Prevalence of Histiocytes and Elevation and Variation of White Cell Count in Blood from Ear Lobe Geneva A Daland Leonard Gottlieb Ralph O Wallerstein and William L Castle (Harvard Med School) did hematologic studies in 10 patients in whom the diagnosis of this disease was established by autopsy and in whom histiocytes were found in the peripheral blood In several instances the finding of histiocytes especially in blood from the ear lobe led to studies that confirmed the suspicion of bacterial endocarditis

Elevation and wide variation in white cell counts together with numerous histiocytes sometimes in the process of phagocytosing red cells may be encountered in bacterial endocarditis in blood samples taken from the ear lobe and sometimes appear in successive drops of blood from this site Such findings are less characteristic of blood samples obtained from the finger tip or the antecubital vein (Fig 74), a point emphasized only in the European medical literature and referred to as the Bittorf phenomenon

This local relative increase in total white cell count which involves all types of white cells as well as the predominance of histiocytes in the blood from the ear lobe in bacterial endocarditis is probably explained largely by the greater selective filtering capacity of the vascular bed of the ear lobe compared to that of the finger tip Histiocytes are larger than other white cells Modern evidence supports the highly

( ) J Lab & Cl M d 48 8 7 845 Decembe 1956

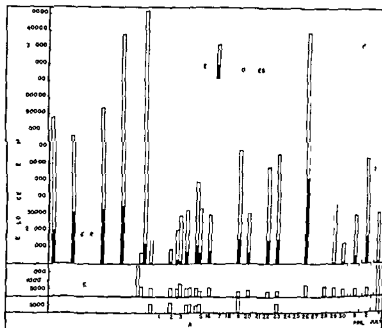


Fig 74—White cell count of blood samples simultaneously obtained from ear lobe, finger tip and antecubital vein. (Courtesy of Daland G A et al J Lab & Clin Med 48 827 845 December 1956)

selective capacity of vascular filters for different types of red cells or particles of even smaller diameter Thus even in normal subjects the total white cell count is greater and the monocyte another large white cell is statistically more common in ear lobe than in finger tip blood (table)

COMPARISON OF AVERAGE TOTAL AND DIFFERENTIAL WHITE CELL COUNTS OF SAMPLES FROM EAR AND VEINS TAKEN SIMULTANEOUSLY IN PATIENT WITH BACTERIAL ENDOCARDITIS (CASE 1 17 OBSERVATIONS) AND IN 10 NORMAL INDIVIDUALS (1 OBSERVATON EACH)

WH B OOD CELLS	R O EA /VE		MEAN CELL DIAMET R (μ)
	Ca I	N m l	
Total counts	70 1	1.3 1	——
Granulocytes	74 1	13 1	13 2
Lymphocytes	78 1	12 1	12 6
Monocytes	93 1	16 1	15 9
Histiocytes	760 1	——	19 7

Ba d m asu eme t f 100 c lls f e h type i sta ned blood fi f m Ca e 1

In addition to the presence of histiocytes the peripheral blood in bacterial endocarditis may show especially in terminal phases of the disease a striking granulocytosis with heavy toxic granulation of the neutrophils Finally a moderate to marked anemia varying from normocytic to macrocytic is usually present in bacterial endocarditis In some patients the elevated reticulocytes and icterus index suggest that this anemia may involve a hemolytic process

The ear lobe provides a desirable site for the preparation of blood films when a search for infrequent abnormal white cells is contemplated as in certain infections or in leukemias especially when leukopenia is present On the other hand blood samples from the finger tip resemble closely those from the antecubital vein and are quantitatively more representative of the white cell content of the circulating blood

Treatment with Cortisone of 22 Cases of Infectious Mononucleosis with Positive Paul Bunnell Reactions is reported by Jean Bernard Georges Mathe and Suzanne Sigal[3] (Paris) Dosage was 100 200 mg in adults and 5 mg /kg body weight in children given for 5 or 6 days No untoward reactions were observed

This therapy is generally effective temperature falls in 24-48 hours and severe angina of ulcerous or pseudomembranous type disappears in a few days Effect of the drug is less definite on adenopathy and splenomegaly but these are also influenced favorably Convalescence is shortened with this treatment and the usual fatigability and weakness characteristic of this phase of the disease are lacking or greatly reduced Blood count and serologic reactions are not affected

Before cortisone no treatment was effective in severe infectious mononucleosis Hence cortisone is indicated in all severe cases with fever extreme weakness and loss of appetite or severe rhinopharyngeal lesions Its indication is more questionable in mild cases although lack of side effects short duration of medication shortening of convalescence and avoidance of asthenia favor its use Usual contraindications to cortisone therapy such as hypertension gastroduodenal ulcer and tuberculosis should be respected despite the short course used Experience shows that cortisone control local symptoms of infectious mononucleosis

(3) S g 545 549 1956

without making concomitant use of antibiotics necessary

► [The risk of disseminating a concomitant or occult bacterial infection must be weighed against the value of reducing systemic intoxication — Ed]

LEUKEMIAS AND RELATED DISORDERS

Cell Free Transmission in Adult Swiss Mice of Disease Having Character of Leukemia is reported by Charlotte Friend[4] (Sloan Kettering Inst) In the course of examination of the Ehrlich ascites mouse tumor with the electron microscope it was noted that the cytoplasm of tumor cells contained particles of constant diameter in close array resembling those seen in virus infected cells A cell free extract of the tumor was prepared and injected subcutaneously into each of 30 Swiss mice less than 24 hours of age After 14 months during which all remained apparently healthy these mice were sacrificed There was no evidence of Ehrlich tumor in any However at autopsy 6 of the 30 mice had enlarged spleens and livers Suspensions of these organs injected intraperitoneally into 6 groups of 5 caused marked enlargement of the spleen and liver in 2 groups Thus a disease with the characteristics of a leukemia was established Later it was found to be serially transmissible in adult Swiss mice by cell free filtrates Thus far the disease has been transmitted through 26 serial passages with filtrates as well as cell suspensions The agent readily passes through Selas 03 Berkefeld N and gradocol membrane filters—these last having an average pore size of 220 mμ Filtrates remain stable when stored for long periods at —70 C or when lyophilized Splenic tissue containing the agent subjected to massive doses of x ray (50 000 r)—far more than sufficient to kill the cells—shows undiminished infectivity The agent is inactivated by heating to 56 C for 30 minutes and by exposure to ether or Formalin

The disease can be transmitted to adult Swiss mice or DBA/2 mice but not to adult PRI, C_3H A $C_{57}P1/6$ or F_1 (*C_{58}×BALB) mice* *Intraperitoneal subcutaneous* intracerebral and intramuscular injections are all effective The

(4) J Exper Med 105 307 318 Ap 1 1957

disease is characterized by marked proliferation of immature mononuclear cells which invade the spleen liver bone marrow kidney and lung and appear in the peripheral blood These large cells can be seen in various stages of mitosis in the organs they infiltrate Terminally the mice have greatly elevated white blood cell counts are anemic and have tremendously enlarged spleens and livers

Though the agent was initially recovered from a diseased Swiss mouse inoculated in infancy with material from the Ehrlich ascites tumor this tumor itself has not appeared in over 400 mice examined after injection with the agent Whether this was latent in the Ehrlich tumor cells or its presence with the tumor was accidental is not clear The possibility of the agent s being the cause of a spontaneous disease which developed during the 14 months observation of the original mouse should be considered

► [The significance of this ob ervation to the student of leukemia is that for the first time a cell free filterable agent has been found to be capable of inducing leukemia when given to adult rather than to newly born mice —Ed]

Character of Agent Inducing Leukemia in Newborn Mice It is possible that leukemia and other neoplasms in animals and man may be caused by filter passing agents derived from tissues This proposition was studied by Jacob Furth Rita F Buffett Maria Banasiewicz Rodriguez and Arthur C Upton[5] with cell free centrifugated or filtered tissue extracts containing the agent prepared from Ak leukemic mice Experiments were designed to investigate whether a virus present in high leukemia incidence inbred strains of mice may be a determinant in leukemia induction by radiation and to establish the sensitivity of different low leukemia strains to the agent in Ak tissue Immunogenetic character of many leukemias (i e whether resembling donor or host) was tested by transplantation assays since one or a few immature or leukemic cells from Ak donors may have been present in the inoculum and survived when grafted in newborn mice giving rise to leukemia close to the leukemia age It was assumed that virus induced leukemias have the immunogenetic character of the recipient strain and cell induced leukemias that of the donor

In the first experiment mice aged less than 12 hours and

(5) F o. Soc E per B l. & Med. 93 16 17 N mb 19 6

some aged 12 24 hours were injected subcutaneously with 0 05 0 1 cc of tissue extract in some instances supplementary *intraperitoneal injections made a total dose of 0 1 cc* Nearly all mice were observed until natural death Implants of leukemic cell suspension in adults were made intramuscularly in the thigh The experiment was terminated when last surviving animals were aged 10 15 months (about 38% were younger than 1 year) Spontaneous leukemias were predominantly thymic and appeared mostly under age 10 months

Tissue extracts from mice of the high leukemia strain Ak injected into newborn mice greatly increased leukemia incidence in Rf DBA/1 and C_3Heb mice and greatly hastened development of leukemia in AkR mice Mortality without gross anatomic manifestation of leukemia was also enhanced in mice of low leukemia strains by injection of extract Although all leukemias in Ak mice were lymphoid with thymic involvement many leukemias in the low leukemia strains were nonthymic Transplantation assays of leukemias induced in low leukemia strains disclosed heterogeneity in types some being related immunogenetically with both host and donor strain Neither salivary gland nor other tumors were induced by the leukemia agent studied

Processes that could explain leukemias following injection of tissue extracts from high leukemia strain mice include transplantation induction and transduction The first can be excluded as a mere occasional complicating factor the latter two merit equal consideration Others have favored induction the present work underlines the theory of leukemic transformation of recipient s cells (transduction) Experiments suggesting it have been described and contradicted and those reported here are not conclusive Nevertheless the theory of transduction based on experiments on pneumococcus transformation would best explain the observed facts necessity of using newborn mice reported high sensitivity of strains which have some genetic relation to the Ak strain noninfectiousness of this agent under natural conditions and the long latency which is about that of the spontaneous disease

In general the following causation of leukemia by virus can be conceived (1) Stimulation of normal cells by intra

cellular specific or nonspecific parasites this would imply that leukemias are virus conditioned neoplasms (2) Induction of somatic mutation by a resident virus proposed by Murphy who named avian tumor viruses mutagens Mutation and abnormal differentiation another possibility imply an irreversible induction change in the cells mutation being genetic and differentiation nongenetic (3) Recombination of chromosomes as with transduction of genetic features of pneumococci and other micro-organisms Presently all these are useful as working hypotheses

***Viral (Egg Borne) Etiology of Mouse Leukemia* Filtered Extracts from Leukemic C58 Mice Causing Leukemia (or Parotid Tumors) after Inoculation into Newborn C57 Brown or C3H Mice** Ludwik Gross[6] (V A Hosp Bronx N Y) presents evidence suggesting that development of leukemia in C58 mice (an inbred strain in which 85% have leukemia after age 6 months) is not spontaneous but caused by a filtrable thermolabile agent presumably a virus transmitted from one generation to another through the embryo

The leukemic agent could be demonstrated by bioassay Filtered (Selas porosity 02 or 03 or Berkefeld [N]) extracts prepared from leukemic C58 donors were inoculated into newborn mice of the very low leukemic C3H (Bittner substrain) or C57 brown (cd) inbred lines Of 128 C57 brown mice inoculated (average 8 hours after birth) 47 (37%) had leukemia at an average age of 10 months Of 20 litter mate controls inoculated simultaneously with heated (70 C for 30 minutes) leukemic extracts or nontreated only 1 had leukemia When filtered C58 leukemic extracts were inoculated into 168 newborn (average 9 hours after birth) C3H mice (Bittner substrain) leukemia developed in 38 (23%) at an average age of 11 months and parotid tumors developed in 12 Of 46 litter mate controls inoculated simultaneously with either heated (70 C for 30 minutes) leukemic extracts or nontreated only 1 had parotid tumors and none had leukemia

Leukemia induced in C57 brown or C3H mice by inoculation of filtered C58-leukemic extracts could be transplanted by cell transfer to adult mice of the recipient line i e C57 brown or C3H but not to mice of the donor (C58) strain

That the leukemic agent was present in normal C58 em

(6) Ca 9 778 91 J ly A g 1956

bryos was evident from experiments in which centrifuged extracts were prepared from normal healthy C58 embryos and inoculated into newborn (average 7 hours after birth) mice of either C57 brown or C3H lines Of 21 C57 brown mice 6 had leukemia and 1 parotid tumors Of 63 C3H mice 6 had leukemia and 7 parotid tumors Fibrosarcomas or myxosarcomas developed in 5 of 19 C3H mice inoculated with cell free extracts of such parotid tumors

Whether one oncogenic agent when inoculated into newborn mice of a susceptible strain may induce leukemia parotid tumors or in some instances soft tissue sarcomas or whether two or three distinct oncogenic agents are present in the C58 leukemic extracts remains to be determined Electron microscope examination of leukemic samples revealed in some instances innumerable spherical particles having a diameter of approximately 30 70 mμ

Treatment of Murine Leukemia with X rays and Homologous Bone Marrow Preliminary Communication D W H Barnes M J Corp J F Loutit and F E Neal[7] (Harwell England) designed experiments to test whether a dose of x rays *sufficient to destroy all normal bone marrow and* lymphatic cells might be completely lethal to leukemic cells and whether the irradiated animal could then be treated with normal isologous or homologous bone marrow for repopulation of hemopoietic and lymphopoietic tissues

A generalized lymphoid leukemia (151/1) of the CBA mouse can be transmitted by passage of 10^6 leukemia cells intravenously or subcutaneously For normal CBA/H mice LD_{50} of x rays is 950 rad in 14 minutes or 1 340 rad spread over 25 hours Intravenous injection of 10^6 leukemia cells was given CBA/H mice one week before irradiation over 25 hours to a dose of 1 500 rad and then treatment usually with isologous bone marrow or infant spleen These mice survived 3 months or longer in three successive experiments

In the first experiment in which leukemia was induced by subcutaneous injection 9 of 10 treated mice survived over 5 months in good condition apparently normal except for gray hair One treated mouse died after 7 weeks of leukemia with a local tumor in the iliac region All untreated controls died in 21 days In the next experiment half the animals were given leukemia subcutaneously All 5 treated mice survived

(7) Brit M J 2 6 6 6 7 S pt 15 1956

well but gray haired In 2 surviving untreated controls leukemia failed to take Of 5 mice given leukemia intravenously 2 treated animals died 1 of generalized leukemia after 19 days and 1 from undetermined cause after 45 days the other 3 were apparently well Controls died in 17 days In the third experiment 3 of 5 animals treated with isologous marrow survived 2 died after 36 and 44 days with generalized leukemia Of 5 mice given homologous marrow from strain A/H mice 3 died 1 2 months after treatment they were wasted and had diarrhea These deaths were attributed to complications of treatment and not to its failure but detailed pathologic processes are not yet understood Of 5 animals treated with T_6/+bone marrow 3 were well and 2 died within 6 days of treatment presumably from effects of radiation Passage of tissues of one of these to 2 normal CBA/H mice failed to reveal leukemia All controls died in 26 days

These preliminary experiments show promise of successful treatment of murine leukemia Results need confirmation with other types of leukemia in other strains of mice and different schedules of treatment may provide more favorable results Limited data in the third experiment bear out previous experience that indicate that for this purpose isologous bone marrow is superior to homologous marrow from related strains

► [Here the leukemic as well a the normal cell are destroyed by the sublethal dose of irradiation Surv val of the mice depends on the recolonization phenomenon by normal myeloid and lymphoid cells of the same inbred strain Does this have a possible application even in the therapy of desperation employed in the present treatment of acute leukem a? Probably not until it is known that "recolonization can take place in h gher or less inbred species and especially that the react ons of the host to the colony can be restrained —Ed]

Lymphomas in Four Siblings In general there is no genetic component of importance in the causation of acute leukemia Only 2 families are recorded with more than 2 siblings affected with malignant lymphoma Anderson in 1951 reported a family in which 5 of 8 were affected with acute leukemia In 1953 Steinberg Farber and Downing reported a family in which 4 of 7 children were affected with acute leukemia or lymphoma

Marlin J E Johnson and Clifford H Peters[8] (Bismarck N D) observed 3 patients with acute leukemia and 1 with

(8) J A M A 163 20 25 J 5 1957

lymphosarcoma in a family of 12 siblings Geographic location exposure to chemicals and to naturally occurring radioactivity were possible etiologic factors However there was insufficient evidence to incriminate them The likelihood of a genetic cause was also investigated by constructing a pedigree and attempting to determine the causes of death among the many relatives of the 4 patients Incidence of malignancies in the other generations was low The possibility that a recessive gene was involved was especially considered because of evidences of consanguinity including the fact that the parents were first cousins The observed patients were thought to present evidence of a genetic component as a cause for leukemia in their family

► [Although the incidence of leukemia in highly inbred strains of mice is clearly subject to genetic influence the heterogeneous genetic background of human stocks is probably a strong deterrent to familial incidence It is therefore especially impressive when the disease occurs among siblings or in both of a pair of identical twins In view of the work of Gross long term follow up of the children born of leukemic mothers would also be of great interest —*Ed*]

Incidence of Leukemia in Ankylosing Spondylitis Treated with X Rays In Nagasaki and Hiroshima the death rate from leukemia has increased as a consequence of the atomic explosions over those cities in 1945 More recently leukemia has been reported in patients irradiated for tumors ankylosing spondylitis enlargement of the thymus and thyrotoxicosis A preliminary report suggests an increased incidence of leukemia and malignant disease in childhood after diagnostic irradiation in utero The establishment of the relationship of leukemia to ankylosing spondylitis with and without irradiation is therefore of unusual importance John D Abbatt and A J Lea[9] examined records of 2 series of patients with ankylosing spondylitis One series of 1 627 men had been treated with x rays the other 399 men had had other treatment

Mean age at death was 39 7 years in the irradiated series and 40 7 in the nonirradiated a difference of no significance However the certified assigned causes of death revealed a gross and obvious excess of leukemic deaths in the irradiated series A high incidence of tuberculosis was observed There was 1 death from aplastic anemia

The expected deaths from leukemia were calculated for persons of comparable groups and compared with those ac

(9) Lancet 1317 13 0 Dec 29 1956

tually observed In the nonirradiated series 0 17 death was expected and none observed In the larger irradiated series 0 33 death was expected and 7 were observed The odds against this excess of deaths being due to chance were greater than 1 000 000 1

It was established that leukemia is associated with ankylosing spondylitis or irradiation or ankylosing spondylitis treated by irradiation The hypothesis that irradiation was the sole cause of leukemia was tested but the data were insufficient to provide a firm answer However in the light of other independent evidence it has been concluded that irradiation plays the main part in the production of the observed cases of leukemia

► [And so the evidence grows How well protected today are your patients your children and your colleagues against unnecessary irradiation? —Ed]

Hodgkin s Paragranuloma There is still much uncertainty among many pathologists and clinicians concerning the existence of this lesion Although first described as early Hodgkin s disease by Jackson in 1937 and given the new name Hodgkin s paragranuloma by Jackson and Parker in 1944 only recently have other investigators added further series of cases On a histologic basis alone C J E Wright[1] reviewed lymphoma cases from the files of the Harvard Cancer Commission and New England Deaconess and New England Baptist hospitals this revealed 10 examples of Hodgkin s paragranuloma (table) Simultaneously 139 biopsy examples of the granulomatous form of Hodgkin s disease were found of which 14 showed a partial resemblance to paragranuloma Autopsy material revealed no paragranuloma Remarkably clinical data on the 10 cases of paragranuloma showed that in all but 1 the disease was localized to one peripheral lymph node region in this patient bilateral involvement in the neck was present All but 1 patient was alive up to 16¾ years after the first biopsy 9 survived over 5 years Two had proved local recurrence and there was possible further manifestation of the disease in 3 others

Histologically the lymph nodes in Hodgkin s paragranuloma showed complete or almost complete loss of normal architecture This was replaced by a packed mass of small lymphocytes producing the picture of lymphocytic lympho

(1) (er 9 73 777 J ly A g 1956

lymphosarcoma in a family of 12 siblings Geographic location exposure to chemicals and to naturally occurring radioactivity were possible etiologic factors However there was insufficient evidence to incriminate them The likelihood of a genetic cause was also investigated by constructing a pedigree and attempting to determine the causes of death among the many relatives of the 4 patients Incidence of malignancies in the other generations was low The possibility that a recessive gene was involved was especially considered because of evidences of consanguinity including the fact that the parents were first cousins The observed patients were thought to present evidence of a genetic component as a cause for leukemia in their family

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(9) Lancet 2 1317 13 0 Dec 29 1956

picture is distinctive and the course relatively benign The disease may be persistent and slowly evolving at least in some cases In others histologic and clinical transitions to typical Hodgkin s disease may occur

Simple Technic for Diagnosis of Nonlipid Histiocytosis Tom D Moore (New York Hosp Cornell Med Center) report on 2 patients with nonlipid histiocytosis (Letterer Siwe disease) proved by biopsy of lymph nodes and by a



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touch preparation of the skin lesions for which the following method was used

TECHNIC—The skin lesion and the surrounding kin were cleansed with Phi ohex® rinsed with sterile saline and wiped relatively dry with a sponge moistened with a solution of Zephiran® The overlying epi lermis was scraped with a scalpel until an exuding surfa e was produced A glass slide was pressed against the lesion at several dif ferent points on the slide After drying the material obtained on the lide was stained with Wright s stain (Fig 75) The large mono nuclear cells demonstrated in this manner were typical of the cells characteristically found by biopsy of the skin lesions in this disease

This technic need not be limited to patients suspected of

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sarcoma or malignant lymphocytoma In some cases there were foci of slightly larger cells apparently lymphoblasts but much smaller than reticulum cells usually with lobulated nuclei sometimes multinucleated and mainly of Reed Sternberg type They seldom reached giant size but might be quite large The cytoplasm was usually moderate in amount and pale staining tending to be eosinophilic The nucleus or nuclei were large in proportion to cell size and the nuclear membrane was well defined with vesicular nucleoplasm in which there was a fine chromatin network

Data on 10 Cases of Hodgkin s Paragranuloma

Sex	Age	Site	Recurrence	Survival after Biopsy
M	22	Neck	None	5 4/12
M	35	Neck	None	16 4/12
M	59	Supraclav	Possible	5 8/12
M	28	Neck	None	2 4/12
M	55	Neck submax	None	12
M	50	Groin	Possible	20 10/12 died
M	34	Neck bilateral	Possible	6 4/12
M	27	Neck	Local	8 6/12
F	49	Axilla	None	16 9/12
F	39	Neck	1 Local 2 Possible further recurrence	13

with slight clumping usually large eosinophilic nucleoli could be seen *Reed Sternberg cells in Hodgkin s paragranuloma are fairly uniform and relatively bland looking* Their distribution was as single cells not uncommonly in groups but rarely contiguous they were usually separated from each other by small lymphocytes They were more common in some regions than others and unless searched for might be missed Mitoses were frequent in these cells and one tripolar example was seen In some cases there were occasional eosinophils and polymorphonuclears in others none There was usually little or no fibrosis and no necrosis was seen

Paragranuloma a rare disease in its true form is probably a phase of Hodgkin s disease in which the histologic

between cellular elements of skin and blood Lymph node biopsies are valuable in diagnosis of leukemic skin lesions since they reveal frankly abnormal cell proliferations which cannot be determined precisely in skin biopsies Usually cell structure in skin and lymph nodes is analogous Some difficulty may arise in chronic lymphoid leukemia where the adenogram is similar to that commonly seen in acute and chronic pruriginous dermatoses

Cutaneous lesions are particularly frequent (some reports give an incidence of 20%) in lymphoid leukemia it is sometimes called the adenocutaneous syndrome Erythroderma and tumors predominate but other lesions may occur Monocytic or histiocytic leukemias resemble lymphoid leukemias clinically and in frequency of skin involvement (10% according to Freeman) however skin lesions sometimes called typical (morbilliform macules ulcerated tumor) are not specific for this type of leukemia Myeloid leukemias rarely show skin lesions usually nodules or tumors Myeloid adenopathies often accompany this type of cutaneous leukemia Exceptionally disseminated tumors containing abnormal plasma cells have been reported in plasma cell leukemias Acute leukemias are accompanied by skin lesions more often than statistics indicate Purpura is often constant mucosal lesions are frequent and tubercles nodules tumors and ulcer are not rare It is sometimes difficult to classify cutaneous leukemias hematologically because of heterogeneity of cells found in the same patient in skin lymph nodes marrow and different viscera

Specificity of Leukemic Skin Reactions is discussed by Peter Wodniansky[4] (Univ of Vienna) Acute as well as chronic leukemia may affect the skin and the mucous membranes The skin changes in lymphoid and myeloid leukemia are similar to each other and are not pathognomonic of a certain type of leukemia However skin affection in myeloid leukemia are rare

The dermatologic changes in chronic leukemias have been classified as specific and nonspecific The former show typical lymphocytic infiltrates and their macroscopic appearance readily suggests leukemia whereas the latter present non characteristic chronic inflammatory changes and may simu

4) W kl W t h 68 440 443 M y 5 1956

having Letterer Siwe disease but theoretically should be of value in any disease entity showing an infiltrative skin lesion characterized by a specific cell type

Since the early lesions of Letterer Siwe disease sometimes resemble seborrheic dermatitis and intertrigo the above technic was applied to 5 ambulatory patients with one or the other of these entities with negative results Touch preparations in these patients revealed only elements of the peripheral blood

► [It would seem worth while to explore the application of this method to the dermal manifestations of other types of leukemia Perhaps there is a useful precedent in the historic transition from surgical to needle biopsy of the bone marrow —Ed]

Histologic and Hematologic Aspects of Cutaneous Lesions in Leukemias According to R Degos B Ossipowski and C Morell[3] (Paris) skin lesions in leukemia are more frequent than hematologic statistics indicate because they are observed chiefly by dermatologists Histologically cutaneous lesions due to direct proliferation of the leukemia are highly characteristic Middle and deep dermal layers contain a massive infiltration of cells belonging to a particular hematic series Density of the mass its often definite inferior border deep perivascular invasion and superficial intact layer immediately suggest a leukemic lesion Although myeloid and leukoblastic cutaneous leukemias (acute leukemias) may consist of an infiltrate of specific cellular elements the much more common lymphoid cutaneous leukemia is manifested only by infiltration of essentially normal lymphocytes In such cases architecture of the infiltrate rather than cellular composition is of diagnostic significance

Cutaneous lesions in leukemias are not all histologically characteristic Some result from localization in the skin of leukemic processes others are nonspecific reactions Anatomicoclinical classification based on histologic criteria is impossible Further histologically specific and nonspecific lesions cannot be correlated with definite clinical findings Histologic examination of skin owing to difficulties in staining does not always permit exact evaluation of cell type in the hematologic sense Cells do not always have the same appearance in blood smears and in skin sections but cytologic methods free of artefacts permit useful comparisons

(3) P e méd 64 1835 1837 N v 7 1956

Autopsy revealed pulmonary hepatic and lymph node metastases of a malignant reticulum cell tumor probably arising in the grossly enlarged mesenteric lymph nodes

Though the cause of idiopathic steatorrhea (as of sprue) is still unknown it is recognized that a small proportion of cases are caused by simple obstruction of mesenteric lacteals by a widespread mesenteric lymphadenitis Ryle described how such obstruction may occur from tuberculous mesenteric nodes with production of the sprue syndrome Fairley and others described a spruelike syndrome in adults associated with lymphoma lymphadenoma and lymphosarcoma of mesenteric nodes caused they suggested by defective intestinal absorption Two of their 4 patients had anemia 1 macrocytic and 1 normocytic

That the patients here described were observed 4 and 2 years respectively without palpable peripheral lymph nodes hepatosplenomegaly or other signs of generalized spread indicates the slow growing relatively benign nature of the neoplastic process These cases were classified in Robb Smith s category of ret culum cell medullary reticulosis (Letterer Siwe syndrome) a condition most frequent in children

Course and Prognosis of Reticuloendotheliosis (Eosinophilic Granuloma Schuller Christian Disease and Letterer Siwe Disease) Study of 40 Cases Mary Ellen Avery John C McAfee and Harriet G Guild[6] (Johns Hopkins Univ) state that only recently have eosinophilic granuloma Schuller Christian disease and Letterer Siwe disease been grouped together on the basis of similar pathologic findings as manifestations of reticuloendotheliosis at different stages of the disease The clinical features however remain distinct except in some transitional cases which have been reported to support the hypothesis of a common underlying process They present 24 men and 16 women with reticuloendotheliosis classified as Letterer Siwe disease Schuller Christian disease and eosinophilic granuloma on the basis of the number and extent of the lesions and their histologic appearance Follow up varied to 43 years

Letterer Siwe disease occurred in infants only Schuller Christian disease was most common up to age 5 years but

(6) Am J M d. 2 636 652 Ap 1 1957

late various skin diseases such as pruritus urticaria chronic eczema erythema exudativum lichen urticatus prurigo petechiae suffusions dermatitis herpetiformis (Duhring) and even pemphigus vulgaris Herpes zoster is also seen with lymphatic leukemia

Many have thought that the nonspecific skin changes have no etiologic relation to leukemia Gates however has proposed that the so called nonspecific leukemic skin changes are due to early histologically not yet discernible leukemic infiltrates Under favorable circumstances these changes may lead to regression of the early infiltrates and later may themselves turn into a quiescent state

Based on recent clinical and histologic observations the author concurs with Gates opinion and suggests that at least some of the nonspecific skin changes in leukemia may be caused directly by the latter

Letterer Siwe Syndrome in Adults Report of Two Cases in which initial symptoms were severe macrocytic anemia with steatorrhea is presented by A W Taylor (Tunbridge Wells England)

CASE 1—Woman 39 pregnant 7 months was seen early in 1947 with severe macrocytic anemia which responded to intensive treatment with transfusions liver and iron A healthy girl was delivered Anemia and weight loss recurred with diarrhea 9 months later Fecal fat was 39 6% Revised diagnosis was idiopathic steatorrhea Response to therapy was satisfactory Except for a troublesome episode of severe generalized eczematous dermatitis in December 1950 anemia and steatorrhea were therapeutically controlled from 1948 to 1951 Back pains and later painful nodules appeared biopsy showed a low grade tumor of lymphatic or reticuloendothelial tissue From mid 1951 to death in May 1952 generalized spread occurred involving peripheral and mesenteric lymph nodes skin and bone At autopsy the mesentery was diffusely infiltrated by necrotic tumor tissue with many grossly dilated lymphatics

CASE 2—Man 39 had severe anemia in 1951 which failed to respond to refined or crude liver preparations but was controlled by folic acid 25 mg daily Despite absence of significant diarrhea fecal fat estimations showed 50% total fat Diagnosis was idiopathic steatorrhea He was in good health on 5 mg of folic acid twice daily until the end of 19 3 when relapse occurred a month after medication was stopped He again responded well to folic acid In March 1954 he had a 2 month history of increasing dyspnea cough fever and weight loss He was severely ill with bronchopneumonia which failed to respond to antibiotics and died a few days later

strated Kesterson and McSwain recorded a 9 year survival in a patient whose initial lesion was a sacral plasmacytoma multiple involvement was not noted until 5 or 6 years later Garland and Kennedy s patient with myeloblastic myeloma was alive 8½ years after onset of symptoms of initial lesion in 8th thoracic vertebra evidence of multiple lesions did not appear for 7 years There was no anemia Bence Jones proteinuria or aspiration of bone marrow in this case

The author s 4 patients had survival periods of 7½ to nearly 13 years 3 had Bence Jones proteinuria from first admission Electrophoresis of urinary proteins in Case 4 showed mobility of gamma globulin reflecting the abnormal peak in the serum Hyperglobulinemia was absent in Case 3 present in Case 4 and probably present in Cases 1 and 2 which showed excessive rouleau formation in blood smears or high sedimentation rate All exhibited well differentiated myeloma plasma cells in the bone marrow Much normal marrow was present in all cases with plasma cell percentages of only 28 12 and 11 in Cases 1 3 and 4 respectively whereas approximately 40% of normal elements remained in Case 2 the only one presenting with appreciable anemia Cases 1 3 followed a classic (though prolonged) course of multiple myeloma with development of osteolytic bone lesions or pathologic fracture or both gradual progession and death In Case 4 significant bone lesions were persistently absent There was no apparent progression after nearly 13 years of disease the patient then aged 76 seemed well Blood urea was normal The spleen and lymph nodes were not palpable but the marrow showed more lymphocytes than plasma cells and numerous tissue basophils or mast cells Age sex long duration absence of osteolytic bone lesions and presence of lymphocytes and mast cells in the bone marrow suggested Waldenstrom s macroglobulinemia but constant Bence Jones proteinuria and absence of anemia bleeding from nose and gums illne s and adenopathy even after 13 years of disease were against this diagnosis Roentgen therapy radiophosphorus stilbamidine urethan intravenous calcium salts and no treatment were used in these cases

► [A rem nder that the bell shaped curve of survival in this as well as n other chronic incurable neoplastic d seases extends well beyond 2 sigmas on either side of the mean value Th s fact obscures prognosis and frustrates interpretation of the effects of therapeutic agents but it does always leave a ray of hope for the individual pat ent—Ed]

was encountered up to age 46 Eosinophilic granuloma though more common in the younger group occurred in 1 patient at age 61 Letterer Siwe disease was present and fatal in 2 cases Schuller Christian was present in 29 with only 4 fatalities The 9 patients with eosinophilic granuloma all recovered Membranous bone defects exophthalmos and diabetes insipidus the classic triad of Schuller Christian disease though among the most common manifestations were *present in combination in only* 3 patient X ray findings particularly of the skeleton supplied the only helpful laboratory aid There were no consistent chemical abnormalities of the blood all serum cholesterol determinations were normal Anemia was rare when present it implied a grave prognosis Eosinophilia in the peripheral blood was notably absent Disturbance in growth occurred in a few patients in whom there was other evidence of pituitary dysfunction Of the 29 patients about one third have recovered about half when last seen still had active disease In patients with eosinophilic granuloma lesions occurred mostly in the bones of the head and pelvis although in no two patients was the same area involved X ray and steroid therapy have been useful in suppressing the lesions of Schuller Christian disease The isolated skeletal lesions of *eosinophilic granuloma have responded to radiation* and to curettage or excision

Long Survival in Multiple Myeloma is discussed by Edwin D Bayrd with 4 case reports Average survival is about 18 months after onset of symptoms but survivals over 5 years have occasionally been reported Of 55 patients followed by Snapper and co workers 8 died in the 5th to 7th year 1 with mature plasma cells in the marrow lived over 8 years The longest survival in Fowler s 52 patients was 3 years Gross and Vaughan reported 2 cases with 6 and 10 year survival respectively One patient a man 66 with multiple radiosensitive lesions proved by biopsy had normal serum globulins and no Bence Jones proteinuria The other a woman 65 had a plasma cell tumor of the mandible removed which recurred after 9 years and caused death a year later There was no Bence Jones proteinuria and no aspiration of bone marrow Multiple myelomatous lesions were not demon

(7) M Clin North America 40 1163 117 July 1956

(SC) of the order of 4 5 and 6 5 S_f and a minor peak of heavy material with SC of about 20 S_f Ultracentrifugation of whole serum from 1 patient with macroglobulinemia showed normal sedimenting proteins and also three fast-sedimenting peaks with SC values of 13 18 and 22 S_f these were absent in corresponding supernatant serum Se um components with SC higher than 16 may have molecular weights of the order of 1 000 000 i e be macroglobulins

In immunologic studies antibodies in rabbits were prepared to macroglobulins from 1 patient normal human serum and gamma globulin Resulting antiserums were then tested with gamma globulin and macroglobulin all gave positive ring and precipitin tests and therefore appeared nonspecific To determine whether macroglobulins possessed any specific antigens antimacroglobulin serum was absorbed with gamma globulin precipitates so formed were centrifuged and the supernatant was tested with macroglobulin Positive precipitin tests obtained suggested an association of specific antigens with macroglobulins The minimum number of antigenic moieties in each antigen solution degree of cross reactivity of various systems and presence of specific antigens in macroglobulin fractions were determined by other technics e g Oudin double diffusion in agar using cells with parallel walls the Ouchterlony plate and immunoelectrophoresis

Although macroglobulins in the serums of 3 patients were present only in gamma globulins by electrophoresis ultra centrifuge and immunologic analyses showed they consisted of separate moieties Antigenic properties in macroglobulins can be used to differentiate them from other fractions of serum globulins Whether macroglobulinemia represents a marked increase in an otherwise normal component of serum protein or is a pathologic protein arising in this disease as an abnormal substance cannot yet be answered with certainty It is possible that both conditions may apply The disea e is most probably a variant of the so called reticuloendotheliose as indicated by the preponderance of mononuclear cells in blood and bone marrow

Differential Diagnosis and Pathogenesis of the Purpuras with Hypergammaglobulinemia or Macroglobulinemia are discussed by N Quattrin E Dini and P Piccoli[9] (*Univ of*

(9) A t m d sc d 156 5 38 1956

Macroglobulinemia Study of Serum Proteins in Four Cases is reported by B Rose L Kovacs S Hanson M Richter J Gordon L Gyenes and A H Sehon[8] (McGill Univ) The patients were 3 women aged 33 40 and 45 and a man 34 Three patients had lymph node and liver involvement and all had large spleens After splenectomy in 1 patient the serum macroglobulins decreased considerably Bleeding tendency was present in 3 patients and all had a reversed albumin globulin ratio by conventional and electrophoretic methods The quantity of macroglobulin varied considerably be



F 76 —Pap elect pho of rum of pat ent w th m r gl lul emia *WS* p t wh le s um *M* m c ogl buln f t n *S* s per at t T e on left a e ta n d w th am do-bl k 10 B for prote d tw on ght w th p od d S h ff g t f c rbohydrate (Court y of Ro e B *et al* T A Am Phy ns 69 139 148 1956)

tween patients The heavy components of macroglobulins showed a variation of 10 6 28 Svedberg units (S_f)

By free electrophoresis the serums of 3 of the patients showed a marked preponderance of globulin in the gamma region After removal of the macroglobulins the supernatant was comparable to normal serum The macroglobulin appeared to be a distinct material confined to the gamma globulin region *Macroglobulins in the serum of the fourth* patient revealed a major component in the gamma region and two minor peaks in the beta and alpha regions Paper electrophoresis yielded similar findings (Fig 76)

In general normal serums are resolved by ultracentrifugation into two major peaks with sedimentation constants

(8) Tr A Am Phys ci n 69 139 148 1956

bone marrow or other organs Macroglobulinemia is not a di ease but a polyetiologic syndrome which appears partic ularly in the course of blastomas and severe liver disease Despite its similarity to multiple myeloma or to chronic aleu kemic lymphomatosis it cannot be confused with them but

DIFFERENTIAL DIAGNOSIS OF HEMORRHAGIC MACROGLOBULINEMIA AND PURPURAS WITH HYPERGAMMAGLOBULINEMIA

S om	H m h c Mac m (W m)	S P p w th Hy g mm m	P H e lo m (Wal m)
Cou se	F tal	S F tal	M ld
Coe ting ll	N pla m h h patoch l g p- thy myl omato- syph lis	Leuk m y lomat h p t p thy l t b ul is	S dos ch c heumat m Sj g vn drom d th
Cl cal feat s	S h m hag diath d m rv t bl th mbo	A n h m h gi m gl b l m	P rp ra f leg
H m t log fi d g	N rmoch m m l k pen w th lymphocytos somet m th m bope d th om bop thia h t d h p rpla f bon m w	A h m h g ma gl b l m	Sl ght h g
El t phor	Hyp p t m w th ema kabl b g mm or t gl bul m	A p rp f W lden t m	M ld hype p o- t m d l hype m m gl b l m
Ult t f g t	Mac ogl b lin (S 16 =S20=20=30 %)	A th p p ra f W lden t m	M gl b l n b ent m m m (1=5 %)
P thogen f h m h g di th	V riou (h pop o- th omb mia o- ton pe d f t of pl t l t ggl t n t th mbocyto- pe)	A hem h gi mac ogl b l m	V sal only

must be regarded as an independent hemorrhagic diathesis Differentiating features of hemorrhagic macroglobulinemia *Waldenstrom s hyperglobulinemic purpura and severe hy*pergammaglobulinemic purpura are shown in the table Hemorrhagic macroglobulinemia is somewhat different from hyperglobulinemic purpura but not from severe purpura with hypergammaglobulinemia The pathogenesis of hyper globulinemic simple purpura is chiefly vascular whereas in

Naples) with reference to 3 cases observed for many years and a review of the literature All 3 cases were characterized by a hemorrhagic diathesis which was severe and polymorphic hepatic changes and a chronic fluctuating course In Case 1 there were encephaloid attacks in Case 2 generalized lymphomatosis due to fibroepithelioid tuberculosis in Case 3 acrocyanosis Syphilis had been present in Cases 1 and 2 Common hematologic findings were a tendency to leukopenia relative lymphocytosis and simple reticular hyperplasia of the bone marrow without infiltration or lymphatic metaplasia Marked anemia was present only in Case 3 A notable increase in gamma globulins (over 80% in Case 3) many positive colloid lability tests absence of cryoglobulins and altered cholesterol levels were common to all 3 cases Electrophoresis showed a large low gamma wave in Cases 1 and 2 and a narrow sharp wave in Case 3 with a high proportion of macroglobulins The condition in Case 3 was typical hemorrhagic macroglobulinemia in the other 2 cases purpura similar to but not to be confused with Waldenstrom s hyperglobulinemic purpura

All hyperglobulinemic purpuras or macroglobulinemias may be classified in four groups (1) Waldenstrom s hyperglobulinemic purpura (2) Waldenstrom s macroglobulinemia ascertained by ultracentrifuge test (3) Waldenstrom s probable macroglobulinemia and (4) severe purpura with hypergammaglobulinemia Waldenstrom s macroglobulinemia affects both sexes Hemorrhagic diathesis is not necessarily present but usually there are polymorphic hemorrhages (especially from the nose mouth and retina) Serum colloid tests are strongly positive cholesterol changes have been noted Electrophoresis shows total hyperproteinemia with marked inversion of albumin globulin ratio caused by a marked increase in gamma globulins Conversely in one third of the cases of hyperglobulinemia beta or zeta globulins were affected The peak of hyperglobulinemia is high and sharp Ultracentrifugation shows increased macroglobulins (average 20 30%) Cryoglobulins and Bence Jones protein are seldom seen Other symptoms are hepatomegaly with hepatocellular insufficiency normochromic anemia with leukopenia and relative lymphocytosis sometimes splenomegaly and adenopathy and nonspecific histioid hyperplasia of the

Treatment of Malignant Lymphoma and Blood Dyscrasias by Conventional Roentgen Therapy Roentgen therapy is founded on years of related experience and should be the basic modality of treatment H B Elkins (Univ of Iowa) is in enthusiastic agreement with those workers seeking to improve results of treatment with new methods and new technics However he feels that until new agents of therapy or new technics have proved their worth and have become widely available our present conventional methods of roentgen therapy for these diseases must continue to be intelligently used In any given case x ray therapy may or may not be the method of choice at a particular stage of its evolution This entire group of diseases is comprised of cases that are highly unpredictable as to prognosis

Localized lymphoma should be treated with moderately heavy roentgen therapy (3 000 3 500 r tumor dose in 2 weeks) There are enough long term survivals with small dosage to cast some doubt on the need for heavier dosage but not enough to warrant its discontinuance

More than one fourth of patients with Hodgkin s disease present widespread involvement but may have no symptoms other than pressure of the enlarged peripheral mediastinal or abdominal lymph nodes Surprisingly small doses of x ray may relieve the symptoms and the doses may be repeated as necessary Nothing is gained by using higher doses or continuing treatment to the point where the involved nodes completely disappear Patients with fever anorexia weight loss pruritus anemia or other systemic signs without significant lymph node enlargement usually do not respond to x ray and are most likely to be benefited by chemotherapy Fair results were formerly noted after total body irradiation and this should be tried in the occasional patient who does not respond to chemotherapy Malignant lymphomas of the reticulum cell type show divergent responses to x ray therapy Those of the skin will respond to as little as 400 r in air but recur near the edge of the previously treated field For generalized disease the apy has consisted of the lowest dosage compatible with satisfactory clinical improvement For mediastinal or retroperitoneal nodes a tumor dose of 600 1 200 r has been satisfactory

( ) Am J Roe g 1 76 960 964 N mbe 1956

macroglobulinemia and severe hyperglobulinemic purpura hemostatic factors are more involved causing a plasmo telangio thrombocytopeno thrombocytopathic picture Qualitative defect in platelets may be determined by lack of agglutination and absence of serotonin (5 hydroxytryptamine)

Diagnosis and Clinical Course of Osteomyelosclerosis J Beyreder and H Rieder[1] (Vienna) studied 11 men and 14 women with osteomyelosclerosis and myelofibrosis In most patients the disease began with tiredness increasing pallor and bleeding in others abdominal swelling was conspicuous Besides a striking pallor the most prominent clinical sign was enlargement of the spleen which often extended to the pelvis The liver was moderately enlarged Occasionally slightly enlarged lymph nodes were noted

The hemogram showed an erythroblastic leukemoid reaction with hypochromic anemia of varying intensity The red blood cell count averaged 3 000 000 The white blood cell count varied greatly though it was usually somewhat increased Thrombocytes were generally decreased in number Bone marrow aspirations if at all successful yielded only a few mature as well as immature cells

X ray bone surveys revealed diffuse sclerosis of the long bones skull pelvis and spine in 6 patients The others had either a normal skeleton or osteoporosis according to age

The diagnosis of osteomyelosclerosis is determined by the presence of aplastic bone marrow the erythroblastic leukemoid peripheral hemogram and the large spleen

The clinical course is usually chronic Treatment is symptomatic Frequent blood transfusions are required in the severely ill X ray treatment is contraindicated No favorable effects from splenectomy were seen

The etiology of this disorder is not clear A connection with polycythemia and active tuberculosis as well as transition into acute myeloid leukemia is not infrequent There is no evidence that it depends on a primary hypertrophy of the reticulohistiocytic system with diminishing hemopoiesis in certain organs It is thought that a fibrosing or sclerosing process of the bone marrow is caused by exogenous or endogenous agents leading to atrophy of the hemopoietic tissue and compensatory extramedullary hemopoiesis

(1) Act h m t 16 99 314 N mb 1956

side effects Depression of cellular elements occurs gradually and can be controlled by periodic blood examination As soon as therapy is interrupted the decline in formed elements has always been reversed

As experience accumulated it appeared that the fall in a patient s leukocyte counts approximated a first order reaction A straight line was obtained on semilog paper when the leukocyte count was plotted on the logarithmic scale and time in days on the linear scale When three white cell counts were available a line could be drawn that within practical limits accurately predicted when the count would decrease to 10 000 which was helpful in estimating the duration of treatment It made little difference whether this was done for total leukocyte counts or absolute lymphocyte counts On completion of treatment rates of response in different patients given the same dose of CB 1348 and in the same patient given different doses were compared by a formula derived from this linear graph

Evaluation of CB 1348 in Hodgkin s Disease and Allied Disorders was made on 42 patients by Bertha A Bouroncle Charles A Doan Bruce K Wiseman and Walter J Frajola[4] (Ohio State Univ) There were 24 with Hodgkin s disease 10 with monocytic leukemia 3 with chronic lymphatic leukemia and 1 each with acute lymphatic leukemia mycosis fungoides multiple myeloma lymphosarcoma and reticulum cell sarcoma

Among the 17 males and 7 females aged 12-64 with Hodgkin disease duration of disease was 3 months to 14 years Twenty three had been previously treated 22 had received deep x ray therapy 11 nitrogen mustard and 6 triethylene melamine (TEM) Three had undergone surgery for complications All except 4 had advanced disease Most had previously failed to respond to x rays nitrogen mustard or TEM or were not suitable for such drugs because of marked depression of the hemopoietic system Administration of p bis (2 chloroethyl) aminophenylbutyric acid (CB 1348) had to be discontinued in 1 patient because of severe nausea 1 other mild nausea Five failed to respond to the first course Two of these were in a terminal stage and were treated only 8 days Three showed some effect in that the general condi

(4) A M A Arch Int Med 97 703 714 J 1956

Lymphatic leukemia is treated by local irradiation of enlarged nodes or by total body radiation as the situation requires In myelogenous leukemia the most common physical finding is a huge spleen X irradiation 100 200 r in air daily *is directed to the spleen to a total of 900 1 200 r or to satis* factory regression

In lymphomas site and extent of the disease are more important in prognosis than is the pathologic picture Many blood dyscrasias may be controlled for a variable time with roentgen therapy alone The patient s symptoms are a satisfactory criterion regardless of the blood count response

► [This article minus its therapeutic details is included because of the merit of its conservative basic philosophy Don t leave the old foxhole until you know of a better one —Ed]

Early Experience with p (N N Di 2 Chloroethyl) Amino phenylbutyric Acid (CB 1348) New Chemotherapeutic Agent Effective in Treatment of Chronic Lymphocytic Leukemia is summarized by S J Altman A Haut G E Cartwright and M M Wintrobe[3] (Salt Lake City) Eight patients (6 males) received 11 courses of therapy The duration of apparent disease ranged from 3 to 93 months Two patients had received no previous treatment 3 had had nitrogen mustard 4 roentgen irradiation and 5 triethylenemelamine The general condition judged by ability to work was poor in 1 fair in 3 and good in 4

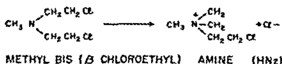
CB 1348 was generally prescribed at a dose level of 0 1 mg /kg /day for first course the dose was 4 9 mg /day for 25 89 days to a total of 168 712 mg Subsequent courses ranged from 3 13 mg daily for 14 42 days for a total of 129 182 mg Maintenance therapy attempted in 1 patient was discontinued because of marked granulocytopenia and a fall in hemoglobin

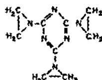
CB 1348 appears effective in controlling certain manifestations of chronic lymphocytic leukemia It causes a decrease in leukocyte count (primarily in lymphocytes but also in granulocytes) reduces the size of enlarged organs and produces considerable subjective improvement It has not produced a consistently favorable hemoglobin or platelet response The drug seems to have a satisfactory margin of safety It can be administered in doses and for sufficient time to control symptoms without causing serious hemopoietic

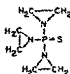
(3) Cancer 9 512 517 May Jun 1956

count was significantly improved and hepatosplenomegaly and lymph node enlargement disappeared Eight other patients in this group obtained good results in that the white blood cell count fell hemoglobin level rose differential count improved and liver spleen and lymph nodes decreased in size Results in lymphocytic lymphosarcoma and Hodgkin s disease were less encouraging although 1 patient with the latter condition showed significant improvement on chlorambucil after resistance to other nitrogen mustards had developed

In patients who respond remissions of 3-6 months may







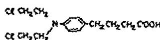


Fig 77 —Stru t l f m l f th t ogen m ta d m thyl-b (β-chl oe h l) m e d l t d mpou d clud g chl amb l (Cou t y f L Jim J E l J.A.M.A 16 178 183 S pt 15 1956)

be obtained with chlorambucil In patients with initial thrombocytopenia chlorambucil appears particularly useful The reason for variability in response is not clear but may be due to differences in gastric acidity absorption or utilization Two patients who showed no response to large doses had moderately low gastric acidity Duration of therapy required with chlorambucil is considerably longer than with triethylene melamine In 1 patient single doses of the latter resulted in remissions of 1 year on two occasions while nearly 2 months of chlorambucil therapy was required for a similar response In the dosages used chlorambucil was practically without side effects

tion and some symptoms improved but for less than 2 months Remissions of 2 4 months were obtained in 9 patients Five of these received a second course of CB 1348 1 had a second remission which lasted 7 months and is receiving a third course 1 had a second remission in progress for only 1 month The other 3 failed to respond to the second course Six patients had a remission of 4 months or longer Three are still in their first remission 3 obtained a remission after a second course One is still in a second remission lasting 7 months One is in the second month of a third remission The other died after failure to respond to a third course of CB 1348 or to x rays The patient with reticulum cell sarcoma and 1 of 9 with monocytic leukemia also had excellent remissions following treatment with CB 1348

Results in 3 patients with chronic lymphatic leukemia were not as satisfactory as reported by Galton perhaps because as a result of previous irradiation treatment the bone marrow had become hypoplastic No benefit accrued to the patients with lymphosarcoma mycosis fungoides and multiple myeloma

As a supplement to x ray therapy CB 1348 is of value in treatment of selected patients with Hodgkin s disease It is safer than TEM It is preferred to nitrogen mustard in some cases because it has practically no side effects and is less damaging to the hemopoietic system

Chlorambucil in Treatment of Chronic Lymphocytic Leukemia and Certain Lymphomas was tried in 30 cases by *John* E Ultmann George A Hyman and Alfred Gellhorn[5] (Columbia Univ) The relation of the aromatic nitrogen mustard chlorambucil (p [di 2 chlorethyl] aminophenylbutyric acid) also called CB 1348 to other alkylating agents is shown in Figure 77 Chlorambucil available in 2 and 10 mg tablets was given orally in all cases with a standard daily dose of about 0 1 0 2 mg /kg body weight an average course consisted of 6 mg /kg and usually lasted 5 7 weeks Three patients were treated for 14 or more consecutive weeks Average total dose was 350 mg total effective dose varied from 50 to 900 mg

Of 18 patients with chronic lymphocytic leukemia 3 obtained excellent results in that the hemoglobin level and white blood cell count returned to normal the differential

(5) J A M A. 162 178 183 S pt 15 1956

pura) Still less frequent (ɔ0 patients) was Henoch s pur pura with visceral bleeding usually manifested by melena and hematemesis Fighteen patients with anaphylactoid purpura had hematuria with albuminuria and at times azo temia and hypertension which aroused suspicion of renal vascular damage In 18 patients there was bleeding into the skin during or after an infection These patients had normal platelet counts Of the other cases of nonthrombopenic pur pura 10 were classified as vascular 2 as factitial 1 as ortho static and 1 as congenital thromboasthenic One case was caused by a drug

Twenty one of the patients with thrombopenic and 10 with nonthrombopenic purpura had a palpable pleen In

DISTRIBUTION OF CASES ACCORDING TO TYPE OF PURPURA 1945 54

			s
Tl l t p p			10
Id p th		78	
A t (l 1	6		
Cl			
S la			
I fect	4		
I 1 t f bo			
	3		
No th l t l p a			8
A pl yl t d		49	
S d		3	
I f t	18		
Otl	15		
T t l			18

only 9 was the enlargement significant Intracranial bleed ing occurred with acute thrombopenic purpura in 5 2 of these died before treatment could be begun Five adolescents and 3 younger girls with thrombopenic purpura had severe vaginal bleeding which was fatal in 1 Hematuria occurred in 18 patients with anaphylactoid (proceeding to chronic nephritis in 1) and in 7 with thrombopenic purpura

Eleven deaths occurred in patients with thrombopenic purpura in 7 the disease was of secondary type In idiopathic cases death was due to hemorrhage in secondary cases to toxic effects of x rays or drugs on bone marrow toxoplasmo sis meningococcemia with adrenal hemorrhage sepsis and intestinal obstruction and toxic nephritis and hepatitis

The outlook for recovery with conservative treatment is good both in nonthrombopenic and in acute thrombopenic

THROMBOCYTOPENIC AND VASCULAR PURPURAS

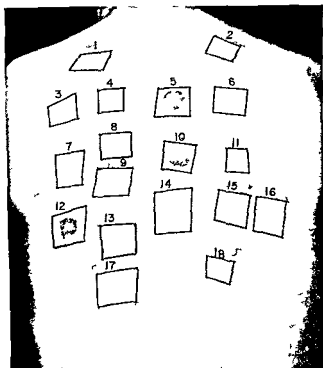
Purpura in Childhood Observations in 187 Cases seen at Mayo Clinic 1945 54 are reported by Stephen D Mills[6] Over half the patients were under age 6 years 3 had purpura of the skin at birth Thrombopenic purpura was present in 105 and nonthrombopenic in 82 The concentration of hemo globin and erythrocyte count were usually normal or de creased depending on the amount of blood lost The leuko cyte count was normal or increased (with infection) Eo sinophilia was noted in both types of purpura but was not striking The erythroid and leukocyte series were normal The bone marrows of 83 patients including several of the nonthrombopenic group showed the megakaryocytes almost universally present in normal numbers but not splitting off platelets normally Eosinophilia of the bone marrow was noted occasionally There was poor correlation between blood platelet count and tendency to bleed Immediately after splenectomy the platelet count usually rose precipitously less often the rise was delayed and in patients with a poor outlook there was no rise Bleeding time was often longer than 30 minutes and clot retraction time over 24 hours Co agulation time was always normal in both categories of pur pura and ruled out hemophilia The Rumpel Leede phenome non or cuff test measuring capillary fragility correlated better with the bleeding tendency than the platelet count

Approximately one fourth of 105 cases of thrombopenic purpura were secondary to infection and of the rest all but 3 due to primary bone marrow involvement were idiopathic Of the idiopathic thrombopenic cases 26 were acute and 52 were of chronic idiopathic type (table)

Of 82 patients with nonthrombopenic purpura about half (49) were of the so called anaphylactoid or allergic type be lieved due to capillary damage by drugs or bacterial aller gens All these had purpura simplex i e bleeding into the skin and oral or nasal mucous membranes In 36 the joints were al o affected with effusion and pain (Schonlein s pur

(6) J P d t 49 306 315 S pt mb 1956

strengths of quinidine sulfate or quinidine sulfate paste were applied The patches were left in contact with the patients arms or backs ½ 48 hours On removal of each patch the skin was examined residual paste or solution removed and a



F g 78 —R ct o bt d w th n gat e p o p t h t t P t t oc rr d ly ont t w th q d p t (5) d 50 100 a d 200 mg /100 ml q in d lf te l t on (14 10 d 1 p t ly) Tru p pu d d n t lt f om onta t w th 15 mg /100 ml q n d lf t l t (6) q d e sulf t p t (7) q l t on (18) phen b b tal p t (3) APC p t (4) d g p te (8) C d lan d (13) p oca m d p t l t on (9 11 d 15) Bt k t l 1 2 16 d 17 (C t y f F dm A L t l J L b & Cl M d 48 0 217 A g t 1956)

positive or negative pressure test of capillary fragility per formed A large number of control drugs and other drugs which the patients were known to have recently ingested produced negative skin tests Only quinidine sulfate paste or strong solutions of it produced positive tests (Fig 78) Cap

purpura Steroid hormone therapy proved disappointing in control of bleeding Splenectomy was performed on 54 of 78 patients with idiopathic thrombocytopenic purpura with ? deaths Autopsy showed massive intraperitoneal hemorrhage but the splenic pedicle was intact and no cause for the bleeding could be found The risk of intracranial bleeding and continuance of purpura into adult life or into menstrual age in girls are determining factors in choice of treatment

► [The apparent failure of ACTH or of cortisone to be at least of temporary benefit in controlling hemorrhage and elevating platelet counts is certainly in contrast to the experience of others —Ed]

Immunothrombocytopenic Purpura Due to Quinidine Report of Four New Cases with Special Observations on Patch Testing is presented by Albert L Freedman Eugene A Brody and Paul S Barr[7] (Montefiore Hosp New York) The 4 patients observed within 7 months had symptoms of thrombocytopenic purpura and all had received quinidine (in various amounts) for heart disorders

Drug induced immunocytopenias have been reported with quinine Sedormid® sulfamethazine Fuadin® and sulfapyridine besides numerous instances due to quinidine In these conditions a serum factor from a sensitized patient can agglutinate and/or lyse appropriate blood cells in the presence of minute quantities of the etiologic drug along with the serum factor blood cell and complement The serum cytopenic factors behave physically and chemically like antibodie and in a few cases complement fixation has been conclusively demonstrated

Idiopathic and drug induced thrombocytopenic purpuras have striking clinical similarities Bone marrow aspirated during active quinidine purpura is generally indistinguishable from that of idiopathic disease A high index of suspicion is necessary to differentiate drug induced from primary thrombocytopenic purpura Diagnosis can be established by special technics such as demonstration of platelet agglutinins clot retraction studies and patch tests for skin (capillary) sensitivity in the presence of the drug The most convenient screening test is based on inhibition of clot retraction of the patient s blood

Patch tests were positive in 2 of the authors patients Patches were made of gauze to which solutions of various

(7) J Lab & Clin Med 48 05 17 Ag t 19 6

This level was surpassed in normal persons receiving doses of 0 6 mg quinidine by mouth in whom blood levels of 2-4 mg/L plasma have been recorded No antigenic relation between platelets and a blood vessel preparation (human choroid plexus) was demonstrated but in the absence of suitable positive controls it cannot be excluded It was not possible to demonstrate passive transfer of local sensitivity with patient s serum and later quinidine intradermally

These experiments gave well defined evidence of an antigen antibody reaction as in Ackroyd s work on Sedormid® purpura Although the antibody seems to be a gamma globulin the nature of the antigen is unclear The antibody does not attach itself to platelets unless quinidine is present quinidine does not attach itself firmly to either platelet or antibody Specific inhibition by a high concentration of quinidine does not occur but otherwise there is an analogy with the artificially conjugated antigens of which Landsteiner s azo dyes were the prototype In these azoprotein antibody reactions the protein moiety conferred antigenicity on the otherwise nonantigenic azodye which Landsteiner termed hapten Specific inhibition was produced when azodye was added to the antibody before carrying out precipitin tests The platelet in quinidine purpura may loosely combine with quinidine and confer antigenicity on it with ensuing antibody formation In vitro this may lead to platelet destruction and the same mechanism may apply in vivo Here the platelet quinidine antibody complex must be stable enough for the reaction to proceed to platelet destruction

Platelets and Vascular Walls in Pathogenesis of Chronic Thrombopenic Purpura J Roskam[9] (Univ of Liege) in discussing the respective roles of the platelets and vascular walls in the pathogenesis of chronic thrombopenic purpuras (hemorrhagic purpuras with significant platelet deficiency) considers whether and to what extent the purpuras are due to impairment of each of these factors alone and together These questions arise in connection with spontaneous hemorrhages and profuse intractable bleeding The duration of the latter makes it more suitable for quantitative study and prognosis in purpura depends especially on the impediment to spontaneous hemo tasis

(9) S g 27 856 866 1956

illary sensitivity in 1 case as revealed by patch tests persisted more than 140 days after the initial episode of quinidine purpura and withdrawal of the drug Maximal capillary damage was produced after 24 hours longer contact produced no further effect

Since this paper was written the authors have observed 2 other patients with quinidine purpura One had a positive and 1 a negative patch test

Thrombocytopenic Purpura Due to Quinidine II Serologic Mechanisms Existing knowledge derives largely from the work of Ackroyd on Sedormid® induced purpura Further information was sought by Frederick G Bolton[8] (Tufts College) in special studies on a patient with a strong concentration of platelet antibody In the presence of quinidine but not of its isomer quinine the antibody in the patient's blood caused platelet agglutination and in the presence of complement lysis of normal platelets and platelets from the patient Complement was fixed when normal platelets quinidine and the patient s serum were incubated with complement When any of the three factors was absent complement was not fixed The factor in serum or plasma could be absorbed by normal platelets only in presence of quinidine Platelets having this absorbed factor were able to fix complement

Normal platelets treated with quinidine and washed with saline could not fix complement in the presence of patient's serum until more quinidine was added quinidine could be dialyzed out readily from a patient s plasma quinidine mixture When platelets having the serum factor and quinidine absorbed on to them were dialyzed against saline the complex of platelet quinidine serum dissociated into its three constituents showing the lability of union among the components The serum factor liberated by this procedure was shown by electrophoresis to be in the gamma globulin fraction To some extent this was confirmed separately by fractionation of the patient s plasma by ammonium sulfate The complement fixing ability of serum factor was destroyed by heating to 65 70 C for 30 minutes

Concentrations of quinidine of the order of 0 3 mg/l caused platelet agglutination with patient s plasma in vitro

(8) Blood 11 547 564 J n 1956

from platelets when blood coagulates might participate in hemostasis by causing direct constriction of vascular smooth muscle surrounding the clot Identification of the vasoconstrictor as 5 hydroxytryptamine (serotonin) has stimulated recent attempts to determine whether this substance fulfills the requirement of a hemostatic agent It was shown that intravenous injection of serotonin abruptly stopped bleeding of peripheral wounds in rats presumably by vasoconstriction as it had no influence on the blood clotting mechanism Others have suggested that platelet serotonin might be a clot retraction principle

Recently it was shown that single large doses of reserpine induced in animals the release of almost all the serotonin from its three major body depots blood platelets intestines and brain B J Haverback T F Dutcher P A Shore E G Tomich L L Terry and B B Brodie[1] (Nat l Inst of Health) investigated whether prolonged administration of reserpine in clinical dosage lowered the concentration of serotonin in platelets of man and if so whether the bleeding time or coagulation mechanism were affected Further they tried to ascertain by animal experiments whether lowering of serotonin in platelets was accompanied by a corresponding decrease in brain serotonin

It was found that daily administration of 1 mg reserpine intramuscularly to man virtually depleted serotonin from platelets within a week After depletion of platelet serotonin bleeding time blood coagulation mechanisms or capillary fragility were not significantly altered These observations suggest that serotonin in the platelets of man has no obvious role in hemostasis Reserpine administered to guinea pigs in daily doses of 0 015 mg/kg body weight completely depleted platelet serotonin in a week but lowered brain serotonin only by about 30%

Thrombocytopenic Purpura Due to Fuadin® (Stibophen) is rare according to Julio V Rivera Hector F Rodriguez and E Perez Santiago[2] (Univ of Puerto Rico) who report an illustrative case

Man 33 with schistosomiasis mansoni had received two courses (40 ml each) of Fuadin® with a month s interval between after each injection of the second series petechiae appeared on his legs

(1) New England J Med 256 343 345 Feb 21 1957
(2) Am J Trop Med 5 863 868 September 1956

The bleeding time of patients with purpura varies greatly according to the site of the incision even when measurements are made simultaneously by one observer The cause of these variations cannot be a general diffuse condition of the blood such as a rarefaction of the platelets Although duration of hemorrhage is prolonged by rarefaction of platelets in the circulating blood it seems unlikely that the thrombopenia of purpura can in itself cause intractable bleeding Another factor must be found to explain spatial variations in bleeding time This factor is apparently a defect in endothelium of the vascular walls which prevents agglutination of platelets The defect termed discrete hemorrhagic endothelitis by the author renders the vascular endothelium less sensitive to the opsonizing effect of the plasma without which the platelets cannot adhere to a foreign surface

Experimental data have proved that to cause intractable bleeding thrombopenia even when pronounced must be associated with vascular lesions or other hematologic disorders such as notable reduction in coagulability That it is possible to cure a severe hemogenic hemorrhagic condition by splenectomy although the patient s blood defects remain unchanged shows that by themselves such defects cannot cause the spontaneous and intractable bleeding of hemorrhagic purpura Thus everything seems to indicate that the other essential vascular factor is the discrete hemorrhagic endothelitis described over 30 years ago by the author

Similarly a vascular factor of some kind—discrete hemorrhagic endothelitis or angiitis—apparently enters into the hemorrhages that appear spontaneously although in them the role of thrombopenia or thrombasthenia seems much less important than in the mechanism of prolonged bleeding Of this purpurigenic factor nothing is known

► [As evidence of a vascular component of thrombopenic purpura independent of the number of platelets is the prompt effect of splenectomy and of ACTH or cortisone in shortening bleeding time and diminishing capillary fragility some hours or days before there is an increase in the number of platelets —Ed]

Serotonin Changes in Platelets and Brain Induced by Small Daily Doses of Reserpine Lack of Effect of Depletion of Platelet Serotonin on Hemostatic Mechanisms In 1912 the concept was advanced that the vasoconstrictor released

Hopkins Univ) A serious and occasionally fatal hemorrhagic disorder has been observed after rapid administration of large amounts of compatible blood Among 40 adults who received 1 or more transfusions thrombocytopenia occurred in the 21 who received more than 14 pints of blood and many of these patients displayed evidences of abnormal bleeding when the platelet count was low In 11 of 19 who received less than 14 pints of blood mild thrombocytopenia but no hemorrhagic manifestations developed

Experiments with auto or homotransfusions of dog blood stored in acid citrate dextrose made it clear that thrombocytopenia occurring after rapid administration of large amounts of stored blood is due to replacement of the blood of the recipient by blood containing nonviable platelets Platelet levels were often lowest at completion of the transfusion The time required for changes to occur in this stored blood that render the platelets nonviable may be short In exchange transfusion in infants blood obtained from a donor only 3 hours before has produced thrombocytopenia promptly in an infant However thrombocytopenia may require 2 days to develop fully suggesting a short survival rather than an immediate destruction of the transfused platelets

In virtually every instance of thrombocytopenia after rapid infusion of blood the platelets did not return to normal until after a lag of 2-6 days Similar delay in restoration of platelets has been noted in a number of other clinical and experimental conditions in which platelets were reduced

The study indicates that use of entirely fresh blood may prevent thrombocytopenia that occurs after massive transfusions

Thrombocytoasthenia and Thrombocytopathia Old Names and New Diseases Hemorrhagic disorders due to qualitative platelet defects have remained obscure even though described years before Thus Glanzmann in 1918 described cases of purpura with normal numbers of platelets but with defective clot retraction Later Willebrand and Jurgens defined a familial disease characterized by purpura prolonged bleeding time and normal clot retraction In 1948 Bernard and Soulier reported a case of purpura with giant lymphocyte sized platelets and later showed that platelet thromboplastin generation was defective According to H

and he had transient bloodstreaking of saliva Similar bleeding occurred after the second and third injections of the third course begun a month later The fourth injection was followed by giddiness general malaise frankly bloody expectorations hematochezia hoarseness and widespread hemorrhagic eruption Liver and spleen were not enlarged and abdomen not distended Platelets were 63 000/cu. mm bleeding time was 18 minutes coagulation time 4 minutes and prothrombin time 11 8 seconds Urine urobilinogen was 1 3 Ehrlich units in 2 hours fecal urobilinogen 280 units in 24 hours

Diagnosis was thrombocytopenic purpura induced by Fuadin® The patient responded to ACTH after a transfusion of fresh blood. Symptoms and signs of schistosomiasis recurred in a few months and were not improved by antispasmodics and gentian violet Fuadin® was started in reduced dosage After the 6th dose (2 5 ml) headache and giddiness developed followed by hemorrhagic eruption of the skin and mucous membranes Platelets were 90 000 bleeding time 3 minutes coagulation time 4½ minutes and prothrombin time 13 seconds Clot did not retract in 24 hours Fecal urobilinogen was 155 Ehrlich units in 24 hours Tourniquet test was positive and Coombs test negative The ECG showed depressed T waves in leads V_{-} V_6 After 2 days of cortisone treatment (which was continued 11 days) no further bleeding occurred and laboratory findings approached normal Increased capillary fragility was demonstrated until the 5th day after onset of purpura Liver biopsy a month after this episode showed fatty infiltration

Administration of 150 ml of plasma from this patient (33 days after the last episode of purpura) to a recipient who had previously received three 5 ml doses of Fuadin® produced thrombocytopenia which reached a maximum after 4 days without purpura Platelet level in the recipient returned to normal by the sixth day Repeated short courses of Fuadin® 10 and 20 days after administration of patient s plasma reproduced the thrombocytopenia A second portion of pla ma from the patient 112 days after the second episode of purpura did not produce thrombocytopenia in the first recipient who received no Fuadin® at this time nor in another who did In vitro studies were also negative Thrombocytopenic purpura in this patient might have been due to occurrence of a drug antibody complex capable of destroying or agglutinating platelets depressing megakaryocyte activity and probably producing capillary damage

► [For a comparable sensitization with respect to a patient s red cells see the article by Harris this YEAR BOOK p 246—Ed]

Mechanism of Thrombocytopenia That Follows Multiple Whole Blood Transfusions was investigated by Dudley P Jackson Julius R Krevans and C Lockard Conley[3] (Johns

(3) T A Am Phy n 69 155 162 1956

In 5 patients characterized as having thrombocytoasthenia electron microscopic examination revealed defective pseudopod formation and lack of spreading (Fig 79) In blood smears platelets were always isolated and clot retraction was manifestly disturbed In the other 18 patients results were less uniform In 5 defined as having thrombocytopathia the platelets remained isolated in blood films appeared large and lymphocyte like in 3 patients but showed normal pseudopod formation and spreading with the electron microscope (Fig 80) Presumably because of chemical



Fig 80 —Gia t platel t f om thrombocytopathia m y spr d ov 20μ n d m t (Courte y f B ter H d P kesch F Blood 11 965 976 No mber 1956)

defects platelet thromboplastin generation and prothrombin consumption were disturbed but all other coagulation factors were normal In the 13 remaining cases defined as probable or possible thrombocytopathia platelet behavior was normal except for an occasional tendency for platelets to be isolated in blood smears Coagulation tests were normal except for temporarily or moderately disturbed platelet thromboplastin generation and prothrombin consumption

Braunsteiner and F Pakesch,[4] examination of the blood of some of such patients with the electron microscope may demonstrate inability of platelets to form pseudopods and to spread when in contact with a wettable surface This is associated with a manifest or latent defect of clot retraction

The normal circulating platelet is round or oval but after a few seconds in contact with a wettable surface it forms numerous pseudopods and spreads out thinly This normal behavior can be altered or abolished by changes in viscosity



Fig 79—C gul t on pl ma fr m th mbocyt the a (Courte y of B a n st H a d Pak sch F Blood 11 965 976 No emb r 1956)

of the medium or by addition of platelet agglutinins or of cocaine and may appear as an inherent defect of the platelets in hemorrhagic disease

The authors carried out electron microscopic examinations of platelets and studies of blood coagulation in 23 patients who presented a uniform clinical picture of severe bleeding from all mucous membranes petechiae and ecchymoses with greatly prolonged bleeding time normal numbers of platelets and normal plasma coagulation factors except occasionally for those related to platelet function There was no detectable circulating anticoagulant Capillary microscopy gave normal results in patients of all three groups

(4) Blood 11 965 976 N embe 1956

The chronic anemia in this patient or the fact that she had a certain degree of alcoholism or both may have produced a hepatic steatosis which gradually developed into cirrhosis The massive fatty degeneration of the liver with occasional fatty cysts found at autopsy resembled those seen in the transformation of steatosis into Laennec s cirrhosis That splenomegaly either isolated or associated with hepatomegaly is common in Rendu Osler disease whereas isolated hepatomegaly *is rare with the hypersplenism in this patient* seemed to show that the involvement of the spleen was primary and that development of the hepatic cirrhosis favored by steatosis of anemic or alcoholic origin was secondary as in Banti s disease The association might be merely fortuitous however hyperplasia of the splenic reticuloendothelial system may have been linked to a change in the endothelial tissue which caused the vascular lesions and led to increased proliferation of reticulohistiocytes at the level of the spleen thus producing clinical hypersplenism

► [Perhaps the hepato plenomegaly occa ionally reported in Rendu Osler s di ease is merely a coincidence with some other condition as here probably with alcoholic cirrhosis and congestive splenomegaly However chronic hypochromic anemia due to blood loss of any type is itself a cause of moderate splenomegaly Splenomegaly on this basis may thus be expected to occur on occasions in Rendu Osler s disease as in any form of chronic recurrent blood loss It i interesting that the author still subscribes to the concept that the splenomegaly of Banti s syndrome i a primary event rather than as now generally accepted the result of increa ed portal or splenic vein pressure —Ed]

COAGULATION DEFECTS

Vascular Hemophilia Familial Hemorrhagic Disease in Males and Females Characterized by Combined Antihemophilic Globulin Deficiency and Vascular Abnormality and apparently transmitted as a mendelian dominant was studied by Irving Schulman Carl H Smith Marion Erlandson Eleanor Fort and Richard E Lee[6] (New York Hosp Cornell Med Center) Affected patients bleed excessively and exhibit markedly prolonged bleeding times in the presence of normal clotting times platelet counts and clot retraction The disease was *originally named pseudohemophilia* by

(6) P I t 18 347 361 S pt mb 1956

Case of Rendu Osler Disease with Hepatosplenomegaly G E Beck and P Magnenat (Univ of Lausanne) discuss the clinical anatomic and pathologic findings in a patient with Rendu Osler disease a condition characterized by cutaneous and mucosal telangiectasias, hemorrhages and a hereditary element The connection between Rendu Osler disease and enlargement of the liver and spleen noted in several reported cases is obscure but telangiectasias angiomas and nevi have often been found in hepatic cirrhosis and other liver diseases

Woman 66 with history of probable chronic alcoholism was hospitalized because of severe anemia and repeated gastrointestinal hemorrhages Since the age of 30 she had noted spots on lips and finger tips that bled easily For years she had bruised easily and had bled abnormally freely from minor wounds Her mother and a maternal uncle had severe epistaxis Examination disclosed typical telangiectasias especially on the palms tongue and lips and small hemorrhagic foci in the retinas Enlargement of the liver and spleen was accompanied by ascites Hematologic studies revealed significant anemia (red cells 1 440 000 and hemoglobin 24%) with leukopenia and thrombopenia Results of liver function tests were generally abnormal The marrow was rich in cells with a highly active red blood cell series and a white blood cell series showing a slight deviation to the left The reticulum and the megakaryocytes were normal The blood group was O X ray of the gastrointestinal tract showed only diverticulosis of the sigmoid Blood transfusions corrected the anemia but the leukopenia and thrombopenia persisted and even increased Two years later she was readmitted in stupor and collapse following massive melena Purulent parotiditis developed and she died in hepatic coma

Besides widespread telangiectasias and enlargement of the liver and spleen autopsy revealed hepatic steatosis and hyperplasia of the reticulohistiocytic system of the spleen This was especially significant because the leukopenia and thrombopenia in the presence of a rich bone marrow with indications of strong regenerative capacity argued for hypersplenism Association of hypersplenism with Rendu Osler disease is rare but may be important in revealing a possible connection between the vascular lesion and the hepatosplenomegaly Thus the vascular malformations and hypocoagulability of the blood due to splenic thrombopenia to which was added hypoprothrombinemia explained the frequency and severity of the patient s hemorrhages She had been advised to undergo splenectomy but refused

(5) H l t m d cta 23 653 65 N ember 1956

22 hours after transfusion coagulation tests were still normal but bleeding time had become abnormal

Since the antihemophilic globulin deficiency is less severe than in classic hemophilia the hemorrhagic diathesis cannot be explained on this basis alone In addition the bleeding time is prolonged in this syndrome contrary to hemophilia in which it is normal Therefore attention was directed to the vascular system Capillary microscopy in the nail beds and bulbar conjunctiva revealed marked coiling of venules striking tortuosity of capillaries and practically no regular capillary loops (Fig 81)

Since transfusion of normal plasma corrected the abnormal bleeding time as well as coagulation abnormalities the vascular dysfunction may result from deficiency of still another factor required for normal vasoconstriction Perhaps administration of normal plasma will correct the bleeding time in patients who have only the vascular abnormality without coagulation defects The von Willebrand syndrome thus includes two kinds of disorder a vascular defect alone and a combination of vascular and coagulation defects

► [For another case report and discussion see the following abstract—Ed]

Pseudohemophilia Type B Hereditary Hemorrhagic Diathesis Characterized by Prolonged Bleeding Time and Decrease in Antihemophilic Factor Karl Singer and Bracha Ramot[7] (Michael Reese Hosp) describe a case and review 19 others previously reported which they believe represent a definite disease entity different from uncomplicated vascular pseudohemophilia

Girl 13 whose parents were first cousins exhibited a severe hemorrhagic diathesis Parents had no relatives known to be bleeders but the patient s older brother had a severe hemorrhagic tendency particularly to epistaxis extensive bleeding after tooth extractions and spontaneous bleeding into skin and muscles Parents said that he suffered from pseudohemophilia with the sole demonstrable abnormality a markedly prolonged bleeding time He died of pneumonia during one of his bleeding episodes

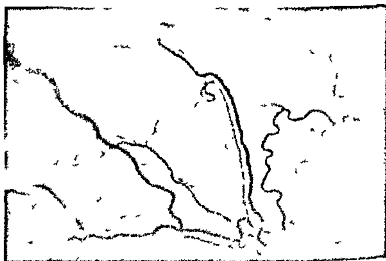
Laboratory studies on the patient revealed prolonged bleeding time normal platelet count and poor prothrombin consumption Thromboplastin generation test and other assays demonstrated marked decrease in antihemophilic factor (AHF) Tentative diagnosis was hereditary thrombopathy (Willebrand s disease) but this was proved wrong by further studies

The same syndrome apparently has been encountered by

(7) A M A A h I t M d 97 715 725 J 1956

von Willebrand and then called constitutional thrombopathy in the belief that a qualitative platelet abnormality was responsible for the abnormal bleeding tendency The disorder is clearly distinguishable from the thrombasthenia of Glanzmann in which bleeding time is normal and clot retraction and platelet morphology abnormal

Prothrombin consumption is also normal further evidence against platelet abnormality No evidence of a defect in the coagulation mechanism has been demonstrated even when



F g 81 —B lbar co ju ct show m ked co l ng and t rt o ty f cap ll ri d ! (C t y of Schulm I *et l* Ped at 18 347 361 S pt mber 1956)

prothrombin consumption and thromboplastin generation tests are used except for a decrease in antihemophilic globulin

The 7 children studied by the authors had hemorrhagic tendencies from early infancy and 1 had intracranial hemorrhage at birth Commonest bleeding site was the nose usually requiring nasal packing and transfusions In several bleeding after dental extraction had continued over a week Excessive bruising was frequent Hemarthrosis occurred in only 2

Normal plasma corrects the defect *in vitro* and plasma transfusions corrected all abnormalities within an hour By

there was no history of abnormal bleeding In each the clotting time of whole blood measured in glass and in silicone coated tubes was greatly prolonged to a degree comparable to that in hemophilia The defect appeared to be localized to early stages of coagulation i e elaboration of thromboplastic activity in shed blood The syndrome could be differentiated from classic hemophilia Christmas disease and deficiencies of plasma thromboplastin antecedent and the fourth thromboplastin component It was possible to prepare a globulin fraction of normal plasma which would correct the patient s defect A similar fraction from the plasma of a patient with this disorder was inert The condition in which this factor appears to be absent has been named Hageman trait after the first patient observed Since 2 of the 3 patients were sisters the defect was probably inherited All 3 were of Germanic stock but there was no evidence that Hageman was related to the 2 sisters

Examination of 44 relatives of the sisters failed to reveal others with this disorder Minor defects in clotting time of whole blood in silicone coated tubes or in recalcified clotting time were found but in each instance a normal concentration of Hageman factor was demonstrated Of the patients 4 grandparents 3 were first cousins Presence of consanguinity and absence of the trait in collateral lines and in children of affected persons are consistent with a hereditary trait carried by a recessive gene Since the defect has been observed in both sexes the gene is apparently not sex linked Hence it appears likely that Hageman trait is transmitted as an autosomal recessive gene

This mode of hereditary transmission of Hageman trait is unique among disorders of the coagulative mechanism Congenital afibrinogenemia parahemophilia and hypoproconvertinemia occur in both sexes and are thought due to transmission of recessive genes but in each in some families individuals presumed to be heterozygous may have partial defects Defects in hemophilia and Christmas disease are transmitted by sex linked recessive genes Deficiency of plasma thromboplastin antecedent is thought due to inheritance of an autosomal dominant gene The hereditary nature of deficiencies of prothrombin and the fourth plasma thromboplastin component is still unclarified

several investigators during the past 2 years 19 similar cases (14 in females) were found though most reports were fragmentary Surprising feature of the syndrome is association of a vascular defect with a decrease in AHF Recently the term hemophilia has lost its sharply defined meaning Classic AHF deficiency cannot be differentiated from plasma thromboplastin component (PTC) deficiency on clinical or genetic grounds alone It has been suggested that the former be called hemophilia A and the latter hemophilia B

Since in the present syndrome AHF is definitely decreased coexistence of a vascular defect and classic hemophilia A may be assumed However the genetic propagation of this disorder is entirely different from the transmission of sex linked hemophilia and resembles closely that of vascular pseudohemophilia This is substantiated by the extraordinarily rare appearance of hemophilia A in the female whereas the vascular pseudohemophilia syndrome occurs commonly (if not preponderantly) in females Schulman and co workers suggest the term vascular hemophilia but the authors prefer the designation pseudohemophilia B which stresses clinical and genetic similarities with vascular pseudohemophilia (vascular pseudohemophilia A) and remind the clinician of this syndrome in all cases with prolonged bleeding time and normal platelet level The most important factor in diagnosis of pseudohemophilia B is knowledge of its existence Many more cases should be observed in the future if serum prothrombin time and thromboplastin generation test are included as routine procedures in all hemorrhagic diatheses In differential diagnosis pseudohemophilia B must be distinguished from uncomplicated vascular pseudohemophilia A from Willebrand s disease (platelet thromboplastic factor deficiency) from sex linked hemophilia A (AHF deficiency) and from hemophilia B (PTC deficiency) Pseudohemophilia B may be transmitted by autosomal genes as mendelian dominants or recessives

Observations on Hereditary Nature of Hageman Trait are reported by Alvin Margolius Jr and Oscar D Ratnoff[8] (Cleveland) Three patients (2 females and 1 male) described in a previous report presented an unusual disorder of blood coagulation which was discovered fortuitously since

(8) Blood 11 565 569 J 1956

lomatous lesions probably due to sarcoidosis In sarcoidosis as in many other conditions glycoproteins are found mainly in the alpha globulin fraction

The changes observed in anaphylactoid purpura were entirely reversible after recovery High percentage values of albumin bound glycoproteins however persisted even after recovery in patients with idiopathic thrombocytopenic purpura and in one with quinidine induced thrombocytopenic purpura Drug induced thrombocytopenic purpura is due to an immunologic mechanism as are many instances of idiopathic disease even when the mechanism may not be demonstrated by in vitro studies Increased glycoproteins and persistent abnormalities of their electrophoretic migration in both pathologic and experimental conditions might be considered indicative of an antibody production mechanism or of permanently altered protein synthesis following stimulation by an antigen

Hemorrhagic Disease with Circulating Inhibitors of Blood Clotting Anti AHF and Anti PTC in Eight Cases were discovered by Jessica H Lewis John H Ferguson and Tulio Arends[1] in a study on single factors in clotting and hemostasis in 240 patients with bleeding tendencies and 160 without Screening tests consisted of determinations of clotting times and reciprocal dilutions of simultaneously drawn fresh normal and patient s bloods or of such recalcified oxalated plasmas Inhibition of coagulation by small amounts of patients blood was regarded as positive Eventually in 5 of 52 hemophiliacs 2 of 26 deficient in plasma thromboplastin component (PTC) and in 1 other circulating inhibitors with anti AHF (antihemophilic factor) or anti PTC activities were demonstrated principally by incubating the patient s plasma with normal plasma and then titrating the AHF or PTC content of the mixture When ordinary hemophilic or PTC deficient plasma was incubated with normal plasma no decrease in AHF or PTC content of the normal plasma was demonstrable In these patients a marked drop in AHF or PTC occurred Even in great dilution plasma of some patients was inhibitory Protamine titrations showed no evidence of heparin or heparin like effects In the idiopathic case both inhibitors primarily anti AHF were present

(1) Bl od 11 846 855 S pt mb 1956

Electrophoretic Distribution of Serum Glycoproteins in Some Hemorrhagic States was determined by Sergio I Magalini Mario Stefanini Margarida Nogueira de Magalhaes Basil Angelopoulos and Sten Kistner[9] (Boston) in 46 patients 33 with idiopathic 2 with thrombohemolytic 4 with quinidine induced 5 with anaphylactoid 1 with combined anaphylactoid and idiopathic thrombocytopenic purpura and 1 with thrombocytopenia caused by platelet agglutinins in prostatic carcinoma Similar electrophoretic studies were made on the serums from 8 healthy fasting subjects 4 patients with lupus erythematosus and 1 with polyarteritis nodosa

Typical glycoprotein migration patterns were found in several bleeding disorders Combined elevation of albumin and gamma globulin bound carbohydrates seemed typical of active idiopathic thrombocytopenic purpura whereas isolated elevation in the albumin bound or gamma globulin bound carbohydrates typified drug induced (quinidine) thrombocytopenic purpura and anaphylactoid purpura respectively Migration of glycoproteins might help in distinguishing some varieties of acute anaphylactoid purpura from rheumatic fever in which glycoproteins are found preferentially in the alpha globulin fraction In collagen disorders a large percentage of carbohydrates migrates with the gamma globulin fraction and there are significant changes in distribution of serum proteins not found in hemorrhagic disorders Consequently glycoprotein studies may help in diagnosis of collagen disorders when they present as thrombocytopenic or anaphylactoid purpura as in the following case

Woman 55 with hemorrhagic purpura had a platelet count of 20 000 Hemostatic tests were consistent with severe thrombocytopenia Paper electrophoresis of serum showed an increase in gamma globulin fraction and predominance of glycoproteins in the gamma globulin region with only a small percentage in the albumin fraction This suggested that the diagnosis of idiopathic thrombocytopenic purpura was unlikely and later a diagnosis of systemic lupus erythematosus was established

In another patient with findings typical of chronic idiopathic thrombocytopenic purpura migration of glycoproteins was predominantly with the alpha globulin fraction which was inconsistent with this diagnosis The spleen was removed because of persistent bleeding and displayed granu

(9) J Lab & Cl n Med 47 9 3 937 J 1956

was found The mechanism whereby platelets can be normal in number—usually also in appearance—and in ability to produce clot retraction but deficient in one or more of their other functions is not clear

► [There is by no means uniformity of opinion concerning the basis of the bleeding tendency in uremia For example Larraine and Langdell found in 3 cases of uremia a prolonged bleeding time and a prolonged clotting time in siliconized glassware No significant deficiency of platelet numbers or functions or of plasma factors and no anticoagulant effects were detected —Ed]

Acute Hemorrhagic Syndrome with Hypofibrinogenemia in Metastatic Cancer was observed in 4 patients by Paul G Frick[3] (Univ of Minnesota) The primary sites were stomach (2) prostate (1) and pancreas (1) In all the hypofibrinogenemia was accompanied by hypoprothrombinemia deficiencies of labile prothrombin conversion factor and antihemophilic globulin and a variable degree of thrombocytopenia Platelet counts were 94 000 56 000 122 000 and 180 000 respectively Stable prothrombin conversion factor and plasma thromboplastin component concentrations were normal The decrease in clotting factors was due to an increased rate of inactivation in the blood stream and not to inadequate synthesis

Although intravascular clotting would best explain changes of coagulation factors autopsy findings give little support to this theory The exact mechanism of the acute disruption of the clotting process in metastatic carcinoma remains unsolved A possible combination of intravascular coagulation and proteolysis would be most consistent with laboratory and autopsy data It is conceivable that intravascular coagulation is immediately followed by fibrinolysis inducing the observed changes of clotting factors without leaving evidence of fibrin clots at autopsy Possibly the same enzyme may induce both processes acting as thromboplastin in low and as fibrinolysin in high concentrations

Onset of hemorrhagic syndrome is usually acute and most patients die of hemorrhage involving the central nervous system Common pathologic features are metastatic involvement of bone marrow and presence of tumor emboli in the pulmonary capillaries Absence of hepatic involvement despite such severe disturbance of blood clotting is of interest All tumors reported have been adenocarcinomas and orig

(3) A t h m t 16 11 29 1956

Possible etiologic factors inducing appearance of circulating inhibitors included repeated transfusions of whole blood and plasma in all and a previous pregnancy in the idiopathic case Two patients showed increases of gamma globulin and presence of inhibitor in 25 33% ammonium sulfate plasma fractions Cortisone therapy was ineffective in 2 cases

Existence of these specific inhibitors typically appearing in severe ca es of the corresponding deficiency diseases probably represents an unusual isoimmunization due to transfusion Lack of response to blood transfusion may suggest presence of an inhibitor although 5 patients had not noted this nor had they any notable increase in clinical symptoms Once an inhibitor has been demonstrated avoidance of future transfusions seems indicated particularly in view of reappearance of anticoagulant in 1 patient s plasma after a small transfusion His titer fell over 6 months to a year on two occasions Another patient showed anti AHF on three examinations over 3 years during which he had received approximately 4 units of plasma How long such inhibitors persist generally is unknown

No indications of why an inhibitor develops were obtained Two patients each had brothers without demonstrable inhibitors but with similar deficiencies each of whom had received about the same number of transfusions or whole blood or plasma (fresh or frozen) All patients who showed inhibitors were severe bleeders apparently completely lacking in the primary factor

Bleeding Tendency in Uremia Jessica H Lewis Marjorie B Zucker and John H Ferguson did hemostatic function studies on 12 patients showing varying degrees of azotemia *with and without hemorrhagic manifestations* Some form of platelet abnormality was found in 11 mild thrombocytopenia was present in 3 and thrombocytopathia in 8 and 4 showed deficiencies of 2 or more of the plasma factors—prothrombin proconvertin proaccelerin or plasma thromboplastin components Almost consistently low serum serotonin values were observed Although this was not necessarily *reflected in prolonged bleeding times* it might explain the general impression that uremic bleeding is vascular in nature No evidence for specific vascular abnormalities

( ) Plood 11 1073 1076 D mb r 1956

probably associated with a fibrinolytic mechanism The second patient recovered dramatically on receiving 4 Gm of human fibrinogen intravenously

Whole blood is almost valueless as a specific therapy for hypofibrinogenemia and should be used only for its bulk cellular constituents and other clotting factors Hypofibrinogenemia should be treated by fractionated fibrinogen intravenously or by triple strength reconstituted dried plasma Estrogen therapy is important in controlling the lytic factor when present Removal of the source of testosterone by orchiectomy has experimental justification beyond the mere need to increase the female over the male hormone Corticotropin has also been claimed to diminish the lysis

► [Any elective operative procedure such as orchiectomy would seem contraindicated as a portal for further hemorrhage until a trial of cortisone and estrogen in large doses had been carried out —Ed]

Coagulation Defects in Severe Intrapartum and Postpartum Hemorrhage Blood loss is a major factor in maternal deaths and morbidity Blood transfusion alone may fail to stabilize the patient s condition The blood clotting mechanism may be upset According to Duncan E Reid Charles C Roby and Albert E Weiner[5] (Harvard Univ) the clotting defect appears to be mainly due to reduced plasma fibrinogen concentation Other factors such as platelets Ac globulin and prothrombin activity may also be reduced but not to hemorrhagic levels An acquired hemorrhagic diathesis resembling hemophilia may develop late in pregnancy or a few weeks to several months after delivery The clotting time of normal blood is prolonged by addition of patient s blood as the result of a circulating anticoagulant believed to interfere with antihemophilic globulin or the precursor of thromboplastin

Most commonly the low fibrinogen concentration is associated with severe forms of premature separation of the placenta but may come from long standing fetal death in utero and amniotic fluid embolism It has been postulated that thromboplastin like substances arising within the uterus reach the maternal circulation producing intravascular clotting and fibrinogen consumption Fibrinolysin has been demonstrated by some observers

A coagulation defect is suspected in patients in the latter

(5) J A M A 161 1244 1247 J ly 28 1956

inated in decreasing frequency in the prostate stomach pancreas or gallbladder

Prognosis is poor but if hemorrhage does not involve a vital organ intensive therapy may be of value The coagulation defect may appreciably fluctuate In treatment administration of fibrinogen should come first this should be supplemented with fresh blood or plasma Prompt therapy requires early diagnosis One cannot wait for results of fibrinogen determination but the sedimentation rate is a helpful index of fibrinogen concentration If hemorrhagic symptoms in metastatic carcinoma are caused by myelophthisic thrombocytopenia only there are a prolonged bleeding time poor clot retraction and a positive Rumpel Leede test If clotting and prothrombin times are prolonged other clotting factors are involved i e the acute hemorrhagic syndrome here described is present

Dangerous Bleeding Associated with Carcinoma of Prostate may occur spontaneously or with surgical procedures especially those directly involving the diseased prostate Variable bleeding may arise from any site particularly the urinary tract and nose and in the skin as ecchymoses If surgery is performed dangerous bleeding may occur in the traumatized area

The relation between bleeding and carcinoma of the prostate has not been fully explained Recent studies of abnormal clotting have shown however that in certain cases of metastatic carcinoma of the prostate fibrinolysis develops and that this is associated at times with a drop in the level of plasma fibrinogen Such fibrinolysis is thought due to proteolytic enzymes which dissolve the clot by digesting fibrin (fibrinolysis) in some cases also lysing fibrinogen (fibrinogenolysis) and other clotting factors such as prothrombin and factor V It has been shown that this proteolytic enzyme is produced by the carcinomatous tissue itself

H T Swan K F Wood and Owen Daniel[4] (Royal Infirm Sheffield) report 2 patients with metastatic carcinoma of the prostate in whom a generalized hemorrhagic state developed During these episodes the blood of both patients was incoagulable owing to a deficiency of plasma fibrinogen In the first patient who died as a result of bleeding this loss was

(4) B M J 1 495 498 M 2 1957

Vitamin K_1 in Treatment of Bishydroxycoumarin Induced Hypoprothrombinemia Comparison of Intravenous and Intramuscular Administration was made by Milton Shoshkes and Arthur J Perelman[6] (Newark N J Beth Israel Hosp) in 20 patients who received anticoagulant prophylactic treatment Nineteen were hospitalized for acute myocardial infarctions and 1 for acute thrombophlebitis of a leg Blood prothrombin times were determined before and 1 2 4 8 and 24 hours after intramuscular injection of 100 mg vitamin K_1 emulsion If the 24 hour prothrombin time was still 50% or less 100 mg of the vitamin emulsion was given intravenously with similar determinations of prothrombin times

Although 6 patients responded to intramuscular injection with a fair depression of previously elevated prothrombin times unpredictability of response to this mode of injection contraindicates its use in emergency situations in which immediate control of an actual or threatened hemorrhage is necessary Intravenous administration is preferred for vitamin K_1 emulsion When the need for counteracting drug induced hypoprothrombinemia is urgent the emulsion must always be given intravenously Shortening of prothrombin time after intravenous injection averaged about 10 seconds and was most marked 8 24 hours after injection

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DRUG ASSOCIATED BLOOD DYSCRASIAS

This section continues the topic included for the first time in the YEAR BOOK OF MEDICINE 1956-57 series It is an attempt by supplying references to articles in the current literature in which drugs are associated with blood dyscrasias to draw this circumstance to the attention of the medical profession Although incomplete the survey may be useful to the physician who must weigh the therapeutic individuality and assets of a drug in the treatment of a particular condition in a particular patient Few useful drugs are completely free of undesirable effects in some patients and reported clinical experience may be helpful in judging the risks

(6) J A M A 161 1145 1147 J ly 1 19 6

weeks of pregnancy seized with moderate to severe abdominal pain usually with vaginal bleeding who enter the hospital in shock The uterus is spastic and tender fetal heart sounds absent weak or irregular Hypofibrinogenemia is detected in one third to one half of such patients The clot observation test is a simple method of recognizing the hypoprothrombinemia Five ml of blood is placed in a clean dry test tube and observed at frequent intervals for clot formation and stability Normal blood will clot in 8 12 minutes and remain intact for 24 hours In the hypofibrinogen states the blood may not clot or if it does it may partially or completely dissolve within 30 60 minutes To confirm the diagnosis the tyrosine method of determining fibrinogen concentration is used

A coagulation defect associated with fetal death in utero is oftentimes heralded by the appearance of ecchymoses and bleeding from the mucous membranes Most instance are associated with Rh incompatibility primarily because this is a common cause of fetal death in utero in the 5th to 8th month The condition is rarely encountered before the 20th week of pregnancy and only in cases in which the dead fetus has remained in utero for more than 5 weeks

Treatment is rupture of the membranes and delivery per vaginam for severe premature separation with coagulation defect The initial problem is to ascertain and manage the clotting defect and combat shock Blood volume must be restored and fibrinogen given intravenously to restore normal levels In the average case the predelivery requirements are 1 500 2 000 ml blood and 4 8 Gm fibrinogen For patients with fetal death in utero the policy should be watchful expectancy controlling the hemorrhagic diathesis by prepartum and intrapartum fibrinogen Until delivery clot observation tests should be done weekly and close observation for bleeding indicated

Because of its low incidence the syndrome of hypofibrinogenemia is sometimes disregarded until the patient is in the terminal stage of hemorrhagic shock If undetected and untreated the patient may die from uncontrolled uterine hemorrhage

Horbaczewski J (Weyburn Sask) Agranulocytosis associated with chlorpromazine therapy (2 cases) Canad M A J 75 412-415 September 1956

James F L and Geesaman R E (Boulder Colo) Agranulocytosis due to phenylbutazone (1 case) Ann Int Med 46 152 155 January 1957

Jeub R P and Michienzi L J (Minneapolis and Saint Paul) Chlorpromazine therapy complicated by agranulocytosis and jaundice (1 case) Minnesota Med 39 740 741 November 1956

Koszewski B J and Hubbard T F (Omaha Nebr) Immunologic agranulocytosis due to mercurial diuretics (1 case) Am J Med 20 958 963 June 1956

Pastor B H and Tetreault A F (Philadelphia) Agranulocytosis and scarlatiniform eruption due to phenindione (1 case) J A M A 161 873 874 June 30 1956

Phemister J C (Edinburgh) Thrombocytopenia and leucopenia following carbutamide (1 case of each) Brit M J 1 199 204 Jan 26 1957

Platzer R F Springs C and Glaser G L (Rochester N Y) Agranulocytosis due to chlorpromazine (2 cases) New York J Med 57 1474 1476 April 15 1957

Pollack B (Rochester N Y) Recurrent thorazine induced agranulocytosis (1 case) Am J Psychiat 113 557 558 December 1956

Schick G and Virks J (Howard R I) Agranulocytosis associated with chlorpromazine therapy (1 case) New England J Med 255 798 802 Oct 25 1956

Simon H J and Rogers D E (New York) Agranulocytosis associated with novobiocin administration Report of a case Ann Int Med 46 778 784 April 1957

Tait G B (York England) Fatal agranulocytosis during carbimazole therapy (1 case) Lancet 1 303 Feb 9 1957

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Tuteur W (Elgin Ill) Fatal agranulocytosis due to chlorpromazine (1 case) Illinois M J 110 236 238 November 1956

Woodward D J and Solomon J D (Washington D C) Fatal agranulocytosis occurring during promazine (Sparine®) therapy (1 case) J A M A 162 1308 1309 Dec 1 1956

Purpura

D Eshougues J R and Griguer P (Algiers) Acute fatal thrombopenic purpura with heterophil platelet agglutinins after absorption of Pyramidon® five months after phenylbutazone treatment (1 case) Sang 27 138 142 1956

Grandjean L C (Copenhagen) Allergic thrombopenic purpura caused by Anti tina® (imidamine chloride) (1 case) Ugesk laeger 118 816 818 July 1956

Green T W and Early J Q (Bristol Tenn) Thrombocytopenic purpura resulting from sulfisoxazole (Gantrisin®) therapy (2 cases) J A M A 161 1563 1564 Aug 18 1956

Mauer A M DeVaux W and Lahey M E (Cincinnati) Neonatal and maternal thrombocytopenic purpura due to quinine (1 case) Pediatrics 19 84 87 January 1957

Symmer W St C (London) Thrombotic microangiopathy (thrombotic thrombocytopenic purpura) associated with acute hemorrhagic leucoencephalitis and sensitivity to oxophenarsine (1 case) Brain 79 511 521 November 1956

It should be emphasized that a reported association between a drug and a blood dyscrasia may not justify the conclusion that the relation is a causal one Repeated association in different patients assumes greater significance and repeated associations in the same patient through rarely observed approach the validity of Koch s postulates —Ed

Aplastic anemia or pancytopenia

ISAACSON S GOLD J A AND GINSBERG V (Brooklyn) Fatal aplastic anemia after therapy with Nuvarone® (3 methyl 5 phenylhydantoin) (1 case) J A M A 160 1311 1312 Apr 14 1956

SHAW R G AND McLEAN J A (Melbourne) Chloramphenicol and aplastic anaemia (7 cases) M J Australia 1 352 358 Mar 16 1957

UNDERWOOD L C (Canton O) Fatal bone marrow depression after treatment with acetazolamide (Diamox®) (1 case) J A M A 161 1477 1478 Aug 11 1956

Megaloblastic anemia

CHRISTENSON W M ULTMANN J E AND ROSEMAN D M (New York) Megaloblastic anemia during primidone (Mysoline®) therapy (1 case) J A M A 163 940 942 Mar 16 1957

FULD H AND MOORHOUSE E H (Liverpool) Observations on megaloblastic anemias after primidone (2 cases) Brit M J 1 1071 1073 May 5 1956

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HOBSON Q J G SELWYN J G AND MOLLIN D L (Isleworth England) Megaloblastic anemia due to barbiturates (1 case) Lancet 2 1079 1081 Nov 24 1956

NEWMAN J D AND SUMNER D W (Manchester) Megaloblastic anemia following the use of primidone (2 cases) Blood 12 183 188 February 1957

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ADAMS J C L CORTI K D F AND HOBSON Q J (Isleworth England) Agranulocytosis and severe leucopenia after chlorpromazine hydrochloride (2 cases) *Brit M J 1 1087 1088 Mar 12 1956*

BERLYNE G M (Manchester) Agranulocytosis due to iodolysin (allyl thiourea ethyl iodide) (1 case) Brit M J 1 495 496 Mar 3 1956

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BRANDON L H (Starkville Miss) Agranulocytosis due to chlorpromazine (1 case) South M J 50 467-468 April 1957

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BURRELL C D (London) Fatal marrow aplasia after treatment with carbimazole (1 case) Brit M J 1 1456 1457 June 23 1956

CRISMON L (Lewiston Ida.) Toxic reaction to Miltown® (Equanil®) (1 case) Am. J Gastroenterol 26 619 November 1956

CORE C P AND BIEZANEK A (Lancs England) Agranulocytosis during treatment with Pacatal (1 case) Lancet 2 1081 Nov 24 1956

THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

TINSLEY R HARRISON MD

PART IV

THE HEART AND BI OOD VESSELS AND THE KIDNEY

CONGENITAL HEART DISEASE

Congenital Cardiac Defects Physician s Guide for Evaluation and Management A report of the Committee on Congenital Heart Disease American Heart Association is presented by Ruth Whittemore S Gilbert Blount Jr Sidney Blumenthal Frank Glenn Edward C Lambert and Helen B Taussig[1] Congenital heart malformations are a major cause of death in infancy Cardiac surgery has been successful in the newborn but the mortality rate is high and it is best to defer operation until childhood However the risk of waiting must be weighed against the operative mortality This decision is difficult and should be made by specially trained physicians The infant should be observed at monthly intervals with special attention to weight gain heart size changing murmurs and cyanosis

If the infant has a normal sized heart is normally active has normal color and gains weight normally special study is not required even though a cardiac defect is diagnosed Further study is indicated promptly if the infant develops dyspnea changing murmurs easy fatigability and increasing cyanosis or polycythemia or fails to gain weight or heart size increases Immediate diagnosis and treatment are indicated if he has paroxysmal dyspnea progressing to syncope progressive cyanosis with dyspnea stridor or choking spells a ventricular rate of over 200/minute lasting hours cerebral vascular accidents cardiac enlargement or cardiac failure Cardiac failure in infants is manifested by rapid respirations heart enlargement gallop rhythm engorgement of the liver rales in the lungs and pitting edema The last two are late signs and ominous

All children and adults suspected of heart disease should

(1) C cul tion 15 631-638 April 1957

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All children and adults suspected of heart disease should

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be given detailed cardiac study Every child with an abnormality should receive a yearly cardiac examination including chest x ray Change in murmurs new symptoms or increase in heart size demand prompt re evaluation Adolescents must be followed closely and evaluation should be prompt if the patient has shortness of breath decreased exercise tolerance cyanosis abnormal rate or rhythm cardiac enlargement or failure changing murmurs hypertension or retarded growth or development

Surgery may be advisable in children with congenital defects For example a continuous murmur over the pulmonary area in a noncyanotic child usually indicates patent ductus arteriosus and it is well to operate before the child enters school A strong pulse in the upper extremities combined with a weak or absent pulse in the lower extremities suggests coarctation of the aorta and surgery should be deferred until age 8 12 Cyanotic children who squat when they are tired usually have pulmonary stenosis and decreased pulmonary blood flow as in tetralogy of Fallot A harsh systolic murmur over the pulmonary area and a weak or absent pulmonic second sound may mean pulmonary stenosis with an intact ventricular septum

Parents should allow the cardiac child to lead as normal a life as possible A cheerful outlook is justified because all anomalies may become amenable to future surgery Immunizations particularly pertussis vaccine should be given at *the usual time Whenever possible the child should* attend a regular school An infant need not be restricted in any way and crying is not harmful

Penicillin should be given prophylactically before dental manipulations or oral surgery Reasonably high concentrations must be available at the time of the dental procedure Combined oral and parenteral administration is preferred and patients should be instructed to report to their physician or clinic should fever develop within a month postoperatively The recommended dosage is 250 000 units 4 times daily for 2 days before surgery on the day of surgery and 2 days after surgery with 600 000 units each of aqueous and procaine penicillin shortly before surgery To patients having genitourinary surgery one of the cycline drugs should be given in full dosage for 5 days beginning 2 days before operation

Most children with cardiac defects tolerate infections as well as normal children except that those with increased pulmonary flow or congestive failure are susceptible to re spiratory infections and may be benefited by long term prophylaxis

Attacks of paroxysmal dyspnea are common in infants with defects which decrease pulmonary blood flow The at tacks are due to anoxemia and not heart failure and are treated by placing the infant in the knee chest position and giving morphine sulfate 1 mg /10 lb body weight and oxy gen if available Polycythemia is common in cyanotic chil dren and is often complicated by cerebral thromboses The latter may be prevented if an adequate fluid intake is pre scribed and dehydration is avoided

Congestive heart failure in infants and children as in adults requires rest oxygen and treatment with digitalis morphine and diuretics in dosages proportional to body weight

Pregnant women with congenital heart defects should be evaluated as early as possible Sterilization is seldom indi cated The critical periods for heart failure parallel the pe riods of maximal load on the circulation i e the 7th and 8th months of pregnancy the later stages of labor and the first postpartum days Unless there are obstetric reasons for it cesarean section is generally contraindicated in patients with any heart disease A woman with a congenital cardio vascular defect has a slightly greater chance of having a child with a congenital abnormality but this chance is so slight that it should not be considered a contraindication to pregnancy

Salient Points in Clinical Diagnosis of Congenital Heart Disease Based on a Nine Year Study of 1 395 Patients In most cases diagnosis can be established without angiocardi ography or cardiac catheterization if the physician correlates the history physical fluoroscopic x ray and ECG findings The differential findings are presented by Benjamin M Gasul and Egbert H Fell (Univ of Illinois)

Coarctation of the aorta is most easily diagnosed by the diminished or absent pulsations in the femoral artery and a differential in pressure in one or both arms as compared

( ) J A M A 161 39 44 May 5 1956

with the legs The murmurs are not characteristic but a systolic murmur is usually present particularly between the scapulae Notching of the ribs is seen in older children or adults Widening of the left lateral superior mediastinal border in the posteroanterior chest film with notching of the ribs is pathognomonic The widening is due to a dilated left subclavian artery

The pathognomonic sign of patent ductus arteriosus is a continuous machinery like murmur maximum over the 2d and/or 1st left interspaces which does not disappear on manipulating the head or jugular vein Fluoroscopic x ray and ECG findings are not characteristic The murmur cannot be differentiated from that of an aortic septal defect and definitive diagnosis depends on retrograde aortography and/or catheterization of the heart

Vascular ring compressing the trachea and esophagus should be suspected if dysphagia wheezing and repeated respiratory infections are present It can be established by x rays with barium swallow

In atrial septal defects a systolic murmur of only moderate intensity is heard maximum at 2d and 3d left interspaces with a reduplicated second pulmonic sound The ECG almost always reveals an incomplete right bundle branch block A mid diastolic rumble is common if the heart is enlarged and usually denotes relative stenosis due to dilatation rather than associated mitral stenosis Fluoroscopy and x rays may be normal if the defect and shunt are small or may show cardiac enlargement a bulge over the pulmonary area increased vascular markings and pulsations if defect and shunt are large Cyanosis is rare

Ventricular septal defects if small are asymptomatic but produce a harsh loud systolic murmur maximum over the 3d and 4th left interspaces with or without a systolic thrill and the second pulmonic sound is normal In large defects there is often a history of pulmonary infections, hyperdynamic apical impulse thrust over the pulmonary area and frequently over the lower parasternal region with a precordial bulge signifying left and right ventricular hypertrophies A systolic thrill and loud systolic murmur are maximum over the 3d and 4th left interspaces and heard better over the 5th than over the 2d The second pulmonic sound i

loud and strong Fluoroscopy and x ray reveal a bulge over the pulmonary area marked increase in pulsations and size of pulmonary vascular markings and usually an enlarged left atrium The ECG reveals predominantly left ventricular hypertrophy or combined hypertrophy

Isolated pulmonary stenosis usually produces no cyanosis except terminally with failure There is a harsh diamond shaped systolic murmur and usually a systolic thrill maximum over the pulmonary area with diminished or absent second pulmonic sound Fluoroscopy and x rays usually reveal a convexity over the pulmonary area but peripheral pulmonary vascular markings and pulsations are diminished The ECG reveals right ventricular hypertrophy If the stenosis is severe early in life cyanosis may be present because of a right left shunt

In aortic and subaortic stenosis there is a harsh systolic diamond shaped murmur maximum over the aortic area with intensity usually proportional to degree of stenosis Systolic thrill is usually present over the same area or felt best over the suprasternal notch The murmur is usually widely transmitted especially over the neck vessels but heard poorly over the lung bases Low systolic and narrow pulse pressures may or may not be present but the arterial pulse curve shows a characteristic slow rise prolonged plateau and slow descent X rays and ECG s may reveal left ventricular hypertrophy in severe cases

Ruptured congenital aneurysm of the sinuses of Valsalva should be suspected if there is sudden onset of chest pain usually with dyspnea and at times with right sided failure accompanied by sudden appearance of a superficial loud continuous systolic and diastolic murmur heard best over the right precordium and transmitted over the precordium with a high pulse pressure Angiocardiography and/or catheterization are helpful

In the tetralogy of Fallot cyanosis is not evident during the first few months of life unless pulmonary stenosis is severe or atresia is present Squatting is common There is usually a systolic thrill and a systolic murmur of varying degree over the 2d 3d and 4th left interspaces The loud second sound over the pulmonic area is due to closure of the valves of the dextroposed aorta Fluoroscopy and x rays re

veal a heart usually not enlarged with the apex elevated a concavity in the pulmonary area and diminished peripheral pulmonary vascular pulsations and markings Poststenotic dilatation of the pulmonary artery may produce a convexity over the pulmonary area The ECG reveals right ventricular hypertrophy

In complete transposition of the great vessels cyanosis is marked Murmurs are not characteristic and may be absent X rays reveal an egg shaped heart (the base narrow) increased pulmonary vascular markings and progressive cardiac enlargement The ECG reveals right ventricular hypertrophy The angiocardiogram is characteristic In the Taussig Bing heart where the aorta is completely transposed and the pulmonary artery over rides both ventricle *fluoroscopy and x rays reveal a bulge over the pulmonary* area and marked increase in the peripheral pulmonary vasculature

In persistent truncus arteriosus with one or two large pulmonary arteries cyanosis is minimal Systolic thrills and murmurs of varying degrees are heard over the 3d and 4th left interspaces Continuous systolic and diastolic murmur may be present over the right or left side of the chest Increased pulmonary markings are present and there is a concavity over the pulmonary area The ECG usually shows right hypertrophy

In the Eisenmenger complex cyanosis is late in onset A systolic thrill and systolic murmur of varying degrees over the 3d and 4th left interspaces and a loud second pulmonic sound are present Fluoroscopy and x rays reveal a bulge over the pulmonary area and increased pulmonary vascular markings The ECG shows right ventricular hypertrophy

Where all the pulmonary veins have an anomalous entrance cyanosis is usually not evident clinically unless the patient is dying Murmurs may or may not be present and are not characteristic If the pulmonary veins enter the superior vena cava the x ray may reveal a characteristic double shadow the figure 8 in the upper mediastinum If they enter the right atrium angiocardiography and/or catheterization are necessary for diagnosis

If a cyanotic patient with a congenital malformation of the heart shows x ray and fluoroscopic evidence of a heart

not definitely enlarged and pulmonary vasculature definitely diminished the congenital malformation probably is amenable to surgical intervention If the heart is definitely enlarged and more important if the pulmonary vascular pulsations and markings are definitely increased surgical intervention is almost never possible in the cyanotic patient

Difficulties in Interpretation of Right Heart Catheterization Data Failure to realize the limitations of cardiac venous catheter data may lead to errors in diagnosis and management of heart disease Noble O Fowler Edgar P Mannix Jr and William Noble[3] (Emory Univ) report 11 instances in which wrong conclusions were drawn from catheter data Correct diagnoses were made at surgery or autopsy

In one patient persistent pulsations of the liver and neck veins recurrent ascites and relative absence of orthopnea suggested tricuspid valve insufficiency and confirming patterns were found by catheter However differences in end diastolic pressures between the right atrium and ventricle suggested additional tricuspid stenosis At autopsy only tricuspid insufficiency and mitral stenosis were found

In another patient a systolic pressure gradient of 68 mm Hg was recorded between the right ventricle and pulmonary artery with the tip of the catheter definitely in the pulmonary artery At thoracotomy a ventricular septal defect was found but no pulmonic stenosis Right ventricular pulmonary artery pressure gradients should be confirmed by repeated passage of the catheter through the valve In this case the catheter tip may have abutted against the artery wall The catheter may become occluded or the high left to right shunt may produce a deceptive gradient across the valve

Several patients who were thought to have patent ductus arteriosus on the basis of blood gas data proved to have ventricular septal defects or other types of arteriovenous fistulas In one the data indicated an atrial septal defect but the continuous murmur suggested a fistula of the sinus of Valsalva emptying into the right atrium confirmed by surgery

The diastolic right ventricular pressure was one third as high as the right ventricular systolic pressure in condition other than constrictive pericarditis Right ventricular sys

(3) \ H rt J 53 343 358 M h 1957

tolic pressures may be somewhat higher than those in the pulmonary artery in the absence of pulmonary stenosis In creased oxygenation of right atrial blood may be produced by a septal defect between the left ventricle and right atrium An increase in oxygen content in the pulmonary artery compared with that in the right ventricle may mean patent ductus arteriosus ventricular septal defect anoma lous pulmonary arteries or contamination of the sample by pulmonary venous blood resulting from a peripheral loca tion of the catheter tip If the pulmonary valve is insufficient the oxygen content of the right ventricle may be higher than that in the pulmonary artery

When the tip of the catheter enters a pulmonary vein after entering the cardiac shadow caution is required in diag nosing whether the pulmonary vein drains into the right or left atrium Wedging the tip into the coronary sinus may produce pressure curves simulating right ventricular pres sure curves Artefacts in right atrial pressure curve due to *motion of the catheter tip may cause falsely high right* atrial systolic pressure reading

Functional Pathology of Pulmonary Vascular Tree in Congenital Cardiac Disease is reviewed by Jesse E Ed wards[4] (Mayo Clinic) In the dynamics of pulmonary cir culation pressure and flow are measurable whereas resist ance is an abstract value derived from a knowledge of the other two Pulmonary artery pressure depends on the vol ume rate of pulmonary flow and resistance to that flow About 25 mm Hg one fifth the systemic arterial pressure is normal

In the normal fetus the pulmonary arterial bed commu nicates freely with the descending aorta by way of the duc tus arteriosus pressures in the pulmonary arteries and aorta and the two ventricles are of the same magnitude *Only* a small proportion of blood leaving the right ventricle enters the pulmonary vascular bed most of it passes through the ductus into the descending aorta Thus the pulmonary vas cular bed must offer a high resistance to flow This high re sistance is in part secondary to the collapsed lung and may in part be due to vasoconstriction of pulmonary arteries and arterioles

(4) Circulation 15 164-196 February 1957

After birth the ductus arteriosus and the foramen ovale close almost simultaneously Thus free communication between the two circuits is eliminated Each circuit then can have its own resistance and pressure without affecting the other Pulmonary pressure becomes lower than systemic pressure and since the same volume of blood flows through each circuit the postnatal fall in pulmonary pressure must represent a decrease in pulmonary vascular resistance By the third month the left ventricle is thicker than the right and pulmonary vessels are thin

In ventricular septal defect the relation of the aorta to the right ventricle is not the primary factor in determining the direction of shunt but rather the height of pulmonary vascular resistance as compared to resistance in the systemic circulation When there is a ventricular defect near the aortic valve the aorta communicates with the right ventricle Perhaps the term Eisenmenger complex should be discarded and this condition described as ventricular septal defect with right to left shunt

In small ventricular septal defects the pulmonary vessels appear normal and calculated pulmonary vascular resistance is normal In all large defects the pulmonary vessels are abnormal in varying degree

There are two basic types of pulmonary vascular patterns in patients with ventricular septal defect Those with high resistance and high reserve have a lowering of pulmonary pressure when the defect is closed which may simply reflect reduced pulmonary flow without change in resistance A fall in pulmonary vascular resistance has not been demonstrated Those who have high resistance low reserve pulmonary vascular beds show a rise or constant high pulmonary pressure after the defect is closed By a comparison of pulmonary vascular and systemic vascular resistance with the patient breathing air and breathing 100% oxygen the high resistance low reserve patients can be separated from those with high resistance and high reserve or those transitional between the two groups Since in the high resistance low reserve cases closing the septal defect may induce abrupt right ventricular failure it is important to predict before surgery if possible the type of vascular bed present

The term tetralogy of Fallot might also be abandoned

because the functional derangement of the same anatomic defect varies from one case to another Such functionally descriptive terms as ventricular septal defect with mild pulmonary stenosis and left to right shunt, ventricular septal defect with moderate pulmonary stenosis and bidirectional shunts or ventricular septal defect with severe pulmonary stenosis and right to left shunt would be more appropriate

In the single ventricle whether anatomic or only functional the basic dynamics are the same as in ventricular septal defect Without pulmonary stenosis pulmonary and systemic pressures are essentially equal and distribution of blood flow depends on relative resistance in the two circulations If systemic resistance is normal, the variable factor is pulmonary vascular resistance When pulmonary stenosis is present the degree of stenosis determines the distribution of blood

The dynamics in patent ductus arteriosus are closely related to those of small ventricular septal defect in most cases A pressure differential exists between the left ventricle and aorta compared to the pulmonary arteries and the pulmonary vascular bed is protected from the pressures of the left ventricle and systemic circulation The small pulmonary vessels are normal If the ductus is so short and wide that no significant pressure differential exists across it regulation of volume and direction of shunt depends primarily on pulmonary resistance and pulmonary vascular changes are similar to those of large ventricular septal defect The two types of vascular bed are seen high resistance high reserve and high resistance low reserve Pulmonary hypertension is always present in the neonatal period Whether or not it persists depends on the size of the patent ductus

In atrial septal defect with low pulmonary vascular resistance and normal pressure and high pulmonary flow the structure of the pulmonary vascular tree is that of a low pressure system including the arterioles The lumens are wide and the walls thin indistinguishable from normal except for tortuosity of the arteries which suggests high flow Patients gradually develop increasing pulmonary vascular resistance and pulmonary hypertension while retaining at least for a time high pulmonary flow Those with moderate

pulmonary hypertension show widely varying patterns in the small muscular arteries and arterioles from vessels that are completely occluded to those that are thin walled and abnormally wide The large muscular pulmonary arteries show medial hypertrophy and small arteries at the beginnings of arterioles exhibit significant occlusive lesions in the form of cellular fibrous intimal thickening Serial sections reveal these lesions to be focal Thus their extent and distribution cannot be appreciated from individual histologic sections

Development of medial hypertrophy of the larger muscular arteries may be a contributing factor in elevated vascular resistance but the intimal lesions of the small arteries and arterioles are peripherally located and seem to be the initiating factor These intimal lesions are probably the result of the high flow which sets up turbulence and abnormal vibrations and may initiate mechanical irritation The intimal cellular fibrous response may be a reparative reaction

Although elevation of total pulmonary resistance results from occlusion of many small arteries and arterioles a high flow characteristically continues and pulmonary artery pressure rises In patients with atrial septal defect with pulmonary arterial pressures near systemic pressure occlusive intimal lesions are present in the large arteries At this stage the pulmonary vascular bed is difficult to distinguish from the high resistance low reserve type seen in ventricular septal defect Necrotizing lesions and subsequent thromboses may further reduce the capacity of the vascular bed These seem to be more common in atrial septal defect with severe pulmonary hypertension than in ventricular septal defect or patent ductus arteriosus

In acquired and congenital mitral stenosis congenital stenosis of the pulmonary veins endocardial sclerosis and chronic failure of the left ventricle from a variety of causes the pulmonary arteries and arterioles show medial hypertrophy Intimal proliferation is seen in normal controls of comparable age but in patients with obstruction to pulmonary venous flow the changes are more severe The basic problem is obstruction to pulmonary venous flow Unless compensating mechanisms exist pulmonary capillary pressure would be the same as pulmonary arterial pressure and

well above that for development of pulmonary edema However, the pressure in pulmonary capillaries is less because of vasoconstriction by thickened arterioles and decreased distensibility of these vessels Pulmonary edema in patients with this functional type of arrangement may be due to temporary failure of a vasoconstrictive phenomenon at the pulmonary arteriolar level and not to heart failure

Clinical and Angiocardiographic Features of Congenital Anomalies of Pulmonary Circulation Classification and Review are presented by Israel Steinberg and Nathaniel Finby[5] (Cornell Univ) Primary dilatation of the pulmonary artery (aneurysm) is rare and can be diagnosed only after all other causes such as pulmonic stenosis congenital and rheumatic heart disease, cor pulmonale heart failure and syphilis are excluded It rarely causes disability and requires no treatment

Isolated valvular pulmonic stenosis is a common congenital anomaly Selection of patients for operation depends on ✓ demonstrating by cardiac catheter severe right ventricular hypertension and pulmonary artery hypotension The right or left main branch of the pulmonary artery may be congenitally absent and diagnosis can often be made by conventional x rays The mediastinum trachea and heart are displaced by an overdistended lung whereas the opposite lung is hypoplastic and poorly visualized Angiocardiography shows an absent main branch of the pulmonary artery with vascularity of the overdistended contralateral lung This condition is usually discovered on routine chest x rays and may be mistaken for a mediastinal tumor When uncomplicated no therapy is indicated but the patient should be carefully observed for respiratory infections

Diagnosis of agenesis of a lung depends on demonstration by bronchography or bronchoscopy of a congenitally absent bronchus and should be suspected if there is an opaque shrunken hemithorax containing the mediastinal structures heart and great vessels without a main bronchu Unless complicated by a congenital cardiovascular anomaly or pulmonary disease it is compatible with normal life

Pulmonary arteriovenous fistulas have recently been recognized during life They are congenital and often related

(5) A g l gy 7 378 394 A gust 1956

to hereditary hemorrhagic telangiectasia Untreated patients may develop vascular thrombosi brain abscesses or fatal hemoptysis Surgical excision is advocated if the fistula is isolated and uncomplicated even in the absence of signs and symptoms

Patent ductus arteriosus is fairly common Ligation is mandatory once the diagnosis is made Reversal of flow however increases the risk of surgery and should be recognized when the characteristic machinery murmur is altered and there are cyanosis and clubbing of the toes and not of the fingers This phenomenon results when pulmonary hypertension is greater than systemic blood pressure producing reversal of blood flow through the ductus which is inserted distal to the origin of the left subclavian artery

When the right pulmonary vein drains into the inferior vena cava conventional x rays show the classic crescentic shadow converging toward the cardiohepatic angle and inferior vena cava which can be confirmed by angiocardiography No treatment is indicated if only one lung is involved The patient is usually asymptomatic When the condition is complicated by other congenital heart lesions surgery may be indicated When the right pulmonary vein inserts into the left innominate a characteristic figure 8 dumbbell silhouette mediastinal mustache or cottage loaf appearance is seen on x ray Angiocardiography shows the shadows on the left to be the dilated common pulmonary venous trunk inserting into the left innominate vein and that on the right to be due to the dilated superior vena cava enlarged because of the increased blood flow from the left innominate vein Total anomalous pulmonary venous drainage inserting into the superior vena cava and right atrium was diagnosed in a girl aged 16 The pulmonary veins could not be reinserted into the left atrium because it was underdeveloped One case was described of anomalous systemic blood vessel insertions into the lung Ligation and division of the aberrant arteries may completely relieve incapacitating dyspnea

Relative Pulmonic Stenosis Impedance to blood flow at a valve orifice can result from a constricted valvular ring the organic form of stenosis or from dilatation of the chamber just proximal to it the relative form Relative

stenosis of the aortic and mitral valves has been repeatedly described but scant attention directed to relative pulmonic stenosis Stephen Contro Robert A Miller and John Derrick[6] (Childrens Mem l Hosp Chicago) analyzed a group of patients who had a pressure gradient across the pulmonary valve but no valvular abnormality

When the gradient was plotted against the estimated pulmonary flow no direct relation could be shown Several patients were studied in whom pulmonary artery flow was several times systemic flow and yet no pressure gradient existed across the pulmonary valve Two patients with a pressure gradient also had mitral stenosis with reduced cardiac output

More likely dilatation of the right ventricle unaccompanied by comparable distention of the pulmonary valvular ring is the principal factor producing relative pulmonic stenosis Increased pulmonary flow may contribute to the genesis of the gradient and its magnitude

Pressure curves inscribed while the catheter is withdrawn from the pulmonary artery into the right ventricle have different contours in organic pulmonic valve stenosis than in relative stenosis Even in the mildest forms of organic stenosis the right ventricular pulse is represented by a dome shaped curve with a peak in midsystole resembling an isometric contraction This is explained by the constant resistance to outflow during ventricular systole since it is entirely produced by a stenotic valve When the valve is normal its opening and closing generate sudden variations in resistance to outflow mirrored in the pressure curve by characteristic angulations The right ventricular pulse presents distinct systolic divisions suggesting a normal mechanism of opening and closure of the valve The normal contour and relatively high pressure of the pulmonary artery curve are added evidence against organic stenosis

Patent Ductus Arteriosus with Reverse Flow Patients with a patent ductus may not have a continuous murmur in infancy in the presence of congestive failure or when severe pulmonary hypertension develops The mechanism of increased pulmonary artery pressure is not understood Predominant flow is through the ductus then from the pul

(6) Am H rt J 53 54 548 Ap l 1957

monary artery to the aorta producing arterial blood oxygen desaturation The resulting clinical syndrome includes cyanosis clubbing polycythemia dyspnea variable cardiac murmurs right ventricular hypertrophy and frequently hemoptysis

Frank London Thomas D Stevenson Andrew G Morrow and J Alex Haller[7] (Nat l Inst of Health) report 3 cases in adults Angiocardiography and cardiac catheterization were of limited value

Each patient had markedly elevated right ventricular pressure with femoral arterial blood desaturation One had a rise in oxygen content of the sample removed from the right ventricle and pulmonary artery indicating a left to right shunt Oxygen saturation in the right brachial and femoral arteries in each patient was higher in the brachial than in the femoral artery which confirmed the finding of patent ductus arteriosus with reverse flow Two patients had normal arterial oxygen saturation in the proximal aorta and a marked drop in saturation at the site of the ductus when retrograde aortic catheterization was done Administration of high concentrations of oxygen did not alter the shunt in these patients In one patient administration of Priscoline® decreased the right to left shunt and at autopsy this patient proved to have a ventricular defect in addition to the ductus

The chief clinical manifestations are dyspnea fatigue hemoptysis precordial pain hoarseness palpitation and right heart failure Important findings are cyanosis clubbing prominence and a systolic lifting of the left hemithorax and an accentuated pulmonic second sound Murmurs are never typical of a ductus Polycythemia is almost always present X ray studies show right ventricular hypertrophy dilated pulmonary arteries and normal to decreased vascularity of the lung The ECG shows right ventricular hypertrophy of the systolic overload type Arterial blood oxygen determinations consistently show less oxygen in the femoral than in the right brachial artery Cardiac catheterization shows pressures in the pulmonary artery either systolic or diastolic equal to or exceeding the aortic pressure

Review of 50 cases (47 from the literature) showed that only 5 patients have lived to age 40 Of 17 operated on in an

(7) South M J 50 160 168 F bru ry 1957

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(6) Am Heart J 53 542 548 Apr l 1957

normal Patients such as these are referred because of heart murmurs not because of symptoms

It was impossible to predict accurately the physiologic disturbance clinically Symptoms physical signs x rays and ECG s were not consistently abnormal in relation to each other or to the size of the shunt or the elevation in pulmonary artery pressure However no patient with right ventricular pressures over 50 mm Hg had a normal ECG

Cardiac Septal Defects—*Ventricular septal defect analysis of 100 cases studied during life* is presented by Daniel F Downing and Harry Goldberg[9] (Philadelphia) Most of the patients were aged 15 years or less the youngest being 3 months and the oldest 52 years Adequate information was available on the period of gestation in 78 In 51 gestation was uneventful 18 mothers had only nausea and vomiting during the first trimester 5 had vaginal bleeding 2 had nausea vomiting and vaginal hemorrhage 1 had severe respiratory infection and 1 had pneumonia None had rubella or other exanthematous diseases

Symptoms in 89 patients could have been cardiac in origin The other 11 were children whose parents had noted nothing abnormal Fatigue in 72 was the most common symptom from tiring easily to inability to perform muscular work longer than a few minutes Dyspnea on exertion was present in 71 and included orthopnea and paroxysmal nocturnal dyspnea in ome Cyanosis was noted at some time in 39 Undoubted cardiac failure had been present in 22 Chest pain had been felt at least three times by 13 Chronic cough was mentioned by 12 paroxysmal rapid heart action occurred in 8 hemoptysis in 6 syncope in 6 and 52 patients perspired profusely Severe respiratory infection had occurred at least once in 33 patients Two patients had had cerebral vascular accidents 1 aged 13 months and the other 41 years

The most frequent physical sign was cardiac murmur systolic alone in 81 diastolic alone in 1 systolic and diastolic in 17 and absent in 1 The greatest intensity of the systolic murmur was at the left sternal border in 91 cases Systolic thrill was present in 65 The second sound at the base to the left of the sternum was accentuated in 68 patients Cardiac

(9) D Ch st 29 475-491 M y 1956

attempt to close the ductus 3 survived the immediate post operative period One died 6 months later the course of 1 is unknown and 1 had a marked decrease in pulmonary artery pressure

The factors which limit the possibility of successful surgery are inability of the heart to tolerate the acute rise in pulmonary artery pressure when the ductus is closed technical problems due to the tense thin walled pulmonary artery and the possibility that the pulmonary arteriolar lesions may not be reversible

Ventricular Septal Defect Analysis of 28 Patients Ventricular septal defect is not a benign lesion and few patients survive to adult life Surgical repair is indicated if evidence of a large shunt or increasing pulmonary hypertension is shown Cardiac catheterization is necessary because the size of the shunt or the degree of pulmonary hypertension cannot be estimated clinically

Harold Margulies John E Gustafson and James T Mc Millan[8] (Des Moines Ia) report their findings in 28 patients aged 4 months to 17 years Growth tended to be poor All had a systolic murmur in the left parasternal area maximal from the 2d to the 4th interspace associated with a distinct thrill Frequently some easy fatigability was shown Two had definite cyanosis on hospitalization for acute pneumonia and associated congestive heart failure None of the others had congestive heart failure

The patients were divided into 4 groups on the basis of catheterization findings normal pressure (under 40 mm Hg) in 5 minimal elevation (40 50 mm Hg) in 5 pulmonary hypertension (over 50 mm Hg) in 10 and pulmonary stenosis and right ventricular pressure (over 50 mm Hg) in 8 Surgery was advised for all patients with pressures over 50 mm Hg To date 16 have had surgery 2 died Four patients still have significant murmurs postoperatively of whom 2 had an infundibular stenosis removed 1 had fibroelastosis and 1 had a large moderator band removed to get at the defect

Five patients had small defects which did not disturb the right side of the heart X rays and ECG s in 3 were so benign it can be predicted their catheterization findings will remain

(8) J Pediat 50 603 608 May 1957

syncope at least once in 18 profuse perspiration in 22 chronic nonproductive cough in 13 and at least one episode of hemoptysis in 8 Cardiac failure had occurred at least once in 43 patients of all ages Subacute bacterial endocarditis was known in 3 24 stated they had had rheumatic fever 26 had had pneumonia and 4 had had cerebral vascular accidents

On physical examination cyanosis was found in 13 patients but was readily apparent in only 4 Prominent pulsations of the carotid were seen in 5 and jugular engorgement in 3 The thorax was asymmetrical in 25 the heart enlarged in 38 a thrill present in 25 atrial fibrillation in 7 gallop rhythm in 5 and pulmonic second sound was accentuated in 86 In 56 patients a systolic murmur alone was heard most often along the left sternal border at the 2d and 3d interspace In 40 patients a diastolic as well as a systolic murmur was heard and in 4 murmurs were absent Moderate clubbing and cyanosis were present in 3

The ECG showed right ventricular hypertrophy in 58% of tracings and right bundle branch block in 21% Five tracings suggested both right bundle branch block and right ventricular hypertrophy On chest films pulmonary vascular markings were increased in 85 and the pulmonary artery was dilated in 81 with cardiomegaly in 83 almost invariably increased to the left

Cardiac catheterization revealed left right shunts of 0 9 L/minute and right left shunts of 0 1 L/minute The highest increase in oxygen content from vena cava to right atrium was 8 9 vol % Arterial unsaturation was present in 25 cases Pulmonary artery and right ventricular hypertension was present in 65 The lower the pulmonary pressure the greater was the amount of blood shunted from left to right The catheter passed from right atrium to left in 25 patients Angiocardiography in 7 patients revealed simultaneous opacification of right and left atria before the contrast substance reached the pulmonary circuit

The mechanism of pulmonary hypertension is the same in atrial and ventricular septal defects However initial and potential flow through an interventricular septum defect is greater than that through one of similar size in the atrial septum There are no characteristic historic or physical findings Right bundle branch block and marked dilatation of the primary branches of the pulmonary artery in a patient

enlargement was evident in 46 cyanosis in 29 clubbing in 14 and associated congenital anomalies in 21

At fluoroscopy nearly half the patients showed increa ed pulsations of the main pulmonary artery and its branches Increased prominence of peripheral pulmonary vasculature was present in 89 patients and the main pulmonary artery was enlarged in 74 Right ventricular hypertrophy was definite or strongly suggested in 59% of ECG s

On cardiac catheterization 90 patients showed a rise in oxygen content of 1 vol % or more from right atrium to right ventricle Arterial oxygen saturation data indicated right left shunt in 34 with saturations below 90% Shunts were calculated in 44 patients and ranged from left right of 11 8 L /minute to right left of 4 4 L /minute Total pulmonary resistance ranged from 66 to 4 800 dyne second/cm^5 and right ventricular work from 0 15 to 15 35 kg /minute The catheter tip passed from right ventricle to aorta in 11 patients Right ventricular and pulmonary artery hypertension was present in 72 patients

Contrary to previous belief ventricular septal defect is significant and most patients have symptoms Cardiac failure occurs relatively early in life in many Pulmonary hypertension is common This is probably due to functional contraction of the small pulmonary vessels as a result of increased pulmonary flow Direction of flow through the defect may change and a constant right left shunt ensue This is the natural history of patients classified as having the Eisenmenger complex a term which should be abandoned Symptoms and physical roentgen and ECG signs of the defect are not characteristic Diagnosis depends on cardiac catheterization supplemented in certain cases by contrast roentgen studies

II Atrial septal defect analysis of 100 cases studied during life was made by Downing and Goldberg[1] Diagnosis of heart disease was not made before age 10 in 34 patients and 17 were aged 25 or more before diagnosis

Five patients had no symptoms 87 had fatigue 90 had dyspnea and many adult patients had paroxysmal nocturnal dyspnea and orthopnea Chest pain was present in 28 paroxysms of rapid heart action in 36 cyanosis at some time in 13

(1) Dis Chest 29 49 507 May 1956

hypertension is relatively infrequent (2) atrial septal defect ostium primum type with valvular insufficiency of both atrioventricular valves or only the mitral valve in which pulmonary hypertension is more frequent and (3) atrial and ventricular defect with atrioventricular valvular insufficiency in which pulmonary hypertension is frequent

Electrocardiographic Studies of Cases with Intracardiac Malformations of Atrioventricular Canal Ely Toscano Barbosa Robert O Brandenburg and Howard B Burchell[3] found the ECG s in 16 cases of defects of the atrioventricular canal proved at operation or autopsy to be uniformly and highly distinctive in differential diagnosis from usual types of atrial septal defect

The characteristic record shows delayed excitation of the right ventricle of the partial right bundle branch configuration in general a left axis deviation and a QRS loop as projected on the frontal plane rotating counterclockwise often placed superior to the isoelectric point In some instances a flattened horizontally disposed figure 8 configuration of the QRS loop in the frontal plane is seen The pattern is modified by pulmonary hypertension and gross left ventricular enlargement caused by mitral insufficiency The P R interval is frequently prolonged

The basic uniformity of the vector pattern tendency to left axis deviation and dominant positive deflection in the unipolar right arm lead make the ECG diagnostic and in particular alert the physician to the possibility that the defect is atrioventricular in a case which otherwise appears as one of typical atrial septal defect The most likely explanation for the ECG features is that the defect at the top of the ventricular septum has fundamentally altered excitation pathways into the ventricles These patterns are not diagnostic or pathognomonic since they may be produced by other heart diseases hypertension and coronary sclerosis

Surgical Treatment of Persistent Common Atrioventricular Canal Report of 12 Cases is presented by Jack C Cooley and John W Kirklin[4] Atrial septal defects in which the anterior inferior margin is formed by a remnant of atrial septal tissue are amenable to repair by several technics Those with no septal tissue between the defect and the atrio

(3) P oc Staff M t M yo Clin 31 513 5 3 Sept. 19 1956
(4) Ib d pp 523 527

with a systolic murmur at the base should arouse suspicion of an atrial septal defect but diagnosis depends on cardiac catheterization

Clinical Features of Persistent Common Atrioventricular Canal are reviewed by Robert O Brandenburg and James W DuShane[2] Although stated to be rare probably 10 15% of defects encountered have been of the common atrioventricular canal variety Since atrial septal defect is the most frequent congenital heart lesion it seems likely that common atrioventricular canal is more frequent than previously recognized particularly in its incomplete or less severe form

It may be a serious lesion as indicated by the frequency of death in affected patients before age 10 months In this respect it resembles ventricular septal defect more than atrial defect However a significant number of patients reach adult life with only mild or moderate symptoms The atrioventricular valves are always abnormal in this defect although there may be no evidence of valvular insufficiency The only significant hemodynamic aberration may be the shunt through the septal defect

Differentiation of this defect from uncomplicated atrial septal defect is important because of the different technics for closing the defects The common atrioventricular canal defect can best be closed by use of the extracorporeal circulation technic

The important clinical feature of persistent common atrioventricular canal is an arteriovenous shunt at the atrial level causing increased pulmonary blood flow In addition there may be a shunt at the ventricular level This and the insufficiency of the mitral valve increase the left ventricular work a condition not present in atrial septal defect The most important physical finding is a harsh murmur along the lower left sternal border at the apex or at both sites related to insufficiency of one or both the atrioventricular valves Two patients had murmurs at the lower left sternal border characteristic of an arteriovenous shunt at ventricular level

Three clinical types of persistent common atrioventricular canal can be defined (1) atrial septal defect ostium primum type without valvular insufficiency hemodynamically identical with atrial septal defect, in which significant pulmonary

(2) Proc Staff M et Mayo Clin. 31 509 513 Sept. 19 1956

last heard from 5 were living 1 had died of chronic heart failure 1 during induction of anesthesia and 2 after cardiac surgery to correct the large right left shunts

In the 71 reported cases of Ebstein s malformation cyanosis was present in 84% and closely paralleled the presence or absence of an atrial septal defect Most patients with cyanosis developed it at birth or early in infancy it was delayed 6 26 years in 37%

The basic deformity of the malformation follows the same pattern The posterior leaflet is displaced downward and is adherent to the ventricular wall to a variable extent and the anterior leaflet forms a long veil like structure The size of the right ventricular chamber and the thickness of its wall vary considerably The right atrium is markedly enlarged The tricuspid orifice may be small and true stenosis present When the heart contracts the tricuspid orifice may be competent with the anterior leaflet pushed against the septum and blood in the right ventricular chamber proper ejected into the pulmonary artery

Characteristics of the auscultatory findings were protean About half the patients reported had both systolic and diastolic murmurs and a third had systolic murmurs only Other heart sounds usually expressed as triple rhythm were noted in about a third The systolic murmurs of varying intensity and quality were usually maximal at or near the apex and the concomitant diastolic murmurs tended to be loudest parasternally in the 2d or 3d left intercostal space

The ECG is usually characteristic Right bundle branch block was present in 45 of the 52 cases in which a tracing was taken Almost all were atypical block with extremely low voltage of the initial deflections and excessive splintering of the R deflections A broad R deflection of low amplitude most evident in leads II and III may be present as a positive wave directly following a normally shaped R wave Atrioventricular conduction defects were observed in 4 patients Paroxysmal supraventricular tachycardia and premature atrial and ventricular extrasystoles occurred in approximately a third of the patients

The cardiac silhouette by x ray tends to present a uniform picture Typically in posteroanterior views the heart is moderately to tremendously enlarged and globular whereas the vascular pedicle is small Angiocardiograms may demon

ventricular valve rings are best considered a form of persistent common atrioventricular canal though often referred to as ostium primum defects

Persistent common atrioventricular canal can be classified as complete or partial The complete form is associated with clefts in the anterior leaflet of the mitral valve and the septal leaflet of the tricuspid valve with a bare area of ventricular septum forming a portion of the lower margin of the defect The partial form has no bare area of ventricular septum and has a defect in only the anterior leaflet of the mitral valve

When diagnosis of common atrioventricular canal has been established surgery is advised unless there is pulmonary hypertension severe enough to cause right left shunt Without surgery a normal life span is unlikely Most patients have symptoms when the lesion is first discovered

Closed technics atrioseptopexy encircling suture and the atrial well technic have not been as successful as open cardiotomy using extracorporeal circulation of blood through a pump oxygenator The cleft in the mitral valve is closed with 5-0 silk sutures and the defect closed by suturing a piece of Ivalon sponge of proper size and shape into it using interrupted 000 silk sutures The first stitch is usually placed through the bare area of ventricular septum anchoring the sponge and subsequent interrupted sutures are placed forward and backward

Of the 12 patients operated on the atrial well technic was used in 3 and extracorporeal circulation in 9 Six were male and 6 female aged 10 months to 27 years Nine survived surgery and all had excellent clinical results Of the 2 who had postoperative catheterization 1 had complete closure of the defect and the other on whom the atrial well technic was used had a 35% residual left right shunt at the ventricular level There were 3 deaths 2 in children aged 10 months and 1 in a boy aged 5 years Causes of death were severe unrelieved mitral insufficiency in 1 and severe pulmonary hypertension in another and the third died shortly after cessation of extracorporeal circulation

Ebstein s Malformation Clinical and Laboratory Study of 9 patients all of whom had cardiac catheterization is presented by Ralph A Kilby James W DuShane Earl H Wood and Howard B Burchell[5] (Mayo Clinic and Found) When

(5) M d ci 35 161 185 Septembe 1956

Hemoglobin was 19 4 Gm /100 ml red blood cells were 6 600 000 and hematocrit 58% Teleroentgenogram revealed cardiomegaly and fluoroscopy confirmed moderate left ventricular enlargement The ECG revealed notching of QRS complexes in standard leads II and III and T wave inversion in leads II III AV_f and V_6 with delay in intrinsic deflection in the left precordial leads

At cardiac catheterization the catheter instead of descending into the right atrium veered and entered the left atrium and left ventricle From the left atrium it could enter all 4 pulmonary veins but not the right atrium When the catheter was introduced through the left femoral vein and inferior vena cava it entered the right atrium normally but could not be introduced into the superior vena cava The impression at this time was of a single vascular anomaly in which the superior vena cava entered directly into the left atrium At surgery findings were confirmed the aorta and left ventricle were enlarged and right atrial appendage hypertrophied and dilated In the pericardium and extending up from the cephalic end of the right atrium was a fibrous remnant of normal superior vena cava The patient died 20 hours after operation

Tricuspid Atresia is an uncommon cardiovascular malformation Isolated cases have been reported in adults but most in infancy or early childhood James W Brown Donald Heath Thomas L Morris and William Whitaker[7] describe 8 patients 7 over age 3 with tricuspid atresia and 1 with congenital tricuspid stenosis Autopsies were made in 4

Characteristic symptoms were breathlessness on exertion cyanosis and recurrent chest infections but these are not confined to tricuspid atresia On physical examination central cyanosis and finger clubbing were present in all and a precordial systolic murmur in all but 1 A palpable thrust at the apex indicated left ventricular hypertrophy in 2 patients but in the others clinical signs were suggestive of Fallot s tetralogy The jugular venous pulse although abnormal in 6 was not diagnostic

An ECG was recorded in 8 patients and showed left axis deviation in all This excluded Fallot s tetralogy and suggested tricuspid atresia Abnormally tall P waves occurred in only 2

Radiologic examination suggested tricuspid atresia in only 2 patients who showed square shaped hearts Generally in tricuspid atresia the cardiac silhouette is compatible with diagnosis of Fallot s tetralogy Angiocardiography provided confirmation in 7 of 8 patients in whom it was done

(7) B t H t J 18 499 518 Oct be 1956

strate the site of the right left shunt and a huge thin walled right atrium may be seen

Cardiac catheterization is usually characteristic Typically the tip of the catheter enters a huge right atrial chamber that occupies the site normally taken by the right ventricle Mean atrial pressure pulses are normal or increased In about half the patients normal right ventricle and pulmonary pressure pulses were recorded at the extreme apex or conus region of the right ventricle Withdrawal of the tip from this site resulted in abrupt transition to atrial pulses In all patients in whom arterial oxygen desaturation indicated right left shunts an atrial septal defect was strongly suspected or shown by direct catheterization angiocardiography or dye dilution curves Only one instance of a ventricular septal defect with Ebstein s malformation has been reported

Most cases of Ebstein s disease are associated with a typical clinical picture the ECG simulates right bundle branch block although the R wave from the right precordium is of low voltage and multiphasic auscultation reveals a double murmur in the left parasternal region perhaps with a loud third heart sound the x ray shows moderate cardiac enlargement with decreased pulmonary vascular markings The phonocardiogram may be characteristic and diagnostic

Superior Vena Cava Draining into Left Atrium Another Cause for Left Ventricular Hypertrophy with Cyanotic Congenital Heart Disease A case is reported by Herman Tuchman John F Brown John H Huston Arvin B Weinstein George G Rowe and Charles W Crumpton[6] (Univ of Wisconsin) Diagnosis can be made by angiocardiography or cardiac catheterization and correction by surgery is feasible

Boy 15 was admitted for fatigue and unexplained fever Cyanosis of finger tips had been noted in childhood and his endurance was limited For 6 months before admission he had afternoon fever easy fatigability shortness of breath and precordial pain with exertion Polycythemia was detected

Physical examination revealed a well developed well nourished boy pulse 88 respiratory rate 20 blood pressure 120/70 temperature 100 F He was plethoric with cyanosis of the acral parts Fingernails were curved down but not clubbed No cardiac murmurs were heard The border of cardiac dulness was at the midclavicular line Liver edge was down 3 cm and the spleen was just palpable

(6) Am J Med 21 481 484 Sept mber 1956

Hemoglobin was 19 4 Gm /100 ml red blood cells were 6 600 000 and hematocrit 58% Teleroentgenogram revealed cardiomegaly and fluoroscopy confirmed moderate left ventricular enlargement The ECG revealed notching of QRS complexes in standard lead II and III and T wave inversion in leads II III AV_f and V_6 with delay in intrinsic deflection in the left precordial leads

At cardiac catheterization the catheter instead of descending into the right atrium veered and entered the left atrium and left ventricle From the left atrium it could enter all 4 pulmonary veins but not the right atrium When the catheter was introduced through the left femoral vein and inferior vena cava it entered the right atrium nor mally but could not be introduced into the superior vena cava The impression at this time was of a single vascular anomaly in which the superior vena cava entered directly into the left atrium At sur gery findings were confirmed the aorta and left ventricle were en larged and right atrial appendage hypertrophied and dilated In the pericardium and extending up from the cephalic end of the right atrium was a fibrous remnant of normal superior vena cava The patient died 20 hours after operation

Tricuspid Atresia is an uncommon cardiovascular malfor mation Isolated cases have been reported in adults but most in infancy or early childhood James W Brown Donald Heath Thomas L Morris and William Whitaker[7] de cribe 8 patients 7 over age 3 with tricuspid atresia and 1 with congenital tricuspid stenosis Autopsies were made in 4

Characteristic symptoms were breathlessness on exertion cyanosis and recurrent chest infections but these are not confined to tricuspid atresia On physical examination cen tral cyanosis and finger clubbing were present in all and a precordial systolic murmur in all but 1 A palpable thrust at the apex indicated left ventricular hypertrophy in 2 patients but in the others clinical signs were suggestive of Fallot s tetralogy The jugular venous pulse although abnormal in 6 was not diagnostic

An ECG was recorded in 8 patients and showed left axis deviation in all This excluded Fallot s tetralogy and suggest ed tricuspid atresia Abnormally tall P waves occurred in only 2

Radiologic examination suggested tricuspid atresia in only 2 patients who showed square shaped hearts Gener ally in tricuspid atresia the cardiac silhouette is compatible with diagnosis of Fallot s tetralogy Angiocardiography pro vided confirmation in 7 of 8 patients in whom it was done

(7) B H rt J 18 499 518 O t be 1956

strate the site of the right left shunt and a huge thin walled right atrium may be seen

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(6) Am J M d. 21 481-484 S pt mber 1956

is the presence of a physiologically significant lesion which produces fatigue shortness of breath syncope ECG evidence of left ventricular hypertrophy pulmonary artery hyperten sion or a systolic gradient of 50 mm Hg or more across the aortic valve with a normal or decreased cardiac output Sur gery should be elected at any time the indications appear There is no optimal age onset of decompensation cannot be predicted and sudden death can occur at any time

The valvular stenosis can be corrected by dilatation of the narrowed orifice with an instrument inserted into the left ventricle Of 19 patients undergoing surgery 1 had an oper ative death 1 died 8 months later 1 was unimproved 1 symp tomatically worse 1 had no symptoms before surgery but 14 experienced relief of symptoms Complications during and after operation were few the procedure was well tolerated

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RHEUMATIC HEART DISEASE

Rheumatoid Aortitis with Aortic Regurgitation Unusu al Manifestation of Rheumatoid Arthritis (Including Spon dylitis) William S Clark J Peter Kulka and Walter Bauer[9] (Boston) review the findings in 22 males aged 18 64 ob served over a 20 year period Syphilis and rheumatic fever were excluded as causative factors in each case In 13 aortic regurgitation became manifest while they were being ob served for arthritis In 9 it was present at the first examina tion Average age at onset of arthritis was 26 and at onset of heart disease 37 Sixteen patients died at an average age of 45

Definite evidence of spondylitis with sacroiliac disease was present in 91% hip or shoulder joints were involved in 86% peripheral joints in 82% and metacarpophalangeal or interphalangeal joints in 50% Uveitis was seen in 59% and 18% had psoriasis Subcutaneous nodules were not observed

Eighteen patients had a significant increase in pulse pres sure 3 had mitral diastolic murmurs (Flint) 9 had aortic systolic murmurs grades I III intensity and 12 had mitral systolic murmurs grades I III intensity Congestive heart

(9) Am J M d 2 580 592 Apr l 1957

Early filling of the left ventricle and a right ventricular window sometimes showing a diminutive right ventricle later are pathognomonic signs in the anteroposterior views Transposition of the great vessels was evident in only 1 patient Cardiac catheterization was performed in 2 It provided anatomic confirmation of an atrial septal defect and suggested tricuspid atresia from inability to introduce the catheter in the right ventricle Generally it is unnecessary for diagnosis

Autopsy in 3 cases showed classic abnormalities of tricuspid atresia and in 1 an associated patent foramen primum Histologic examination showed the small pulmonary vessels to be normal in the youngest patient aged 3 months but in another aged 7 years the vascular bed was reduced because of extensive thrombosis in pulmonary arteries and veins Anastomotic operations are more likely to be successful when done in infancy before secondary pulmonary vascular changes develop

Congenital Aortic Stenosis Clinical Aspects and Surgical Treatment are reviewed by Daniel F Downing[8] (Hahnemann Med College) in 29 boys and 8 girls The most common accompanying abnormality was coarctation of the aorta in 8 Pulmonary stenosis was found in 4 and patent ductus arteriosus in 1

A loud harsh systolic murmur in the 2d and 3d interspaces near the sternum transmitted to the neck vessels and accompanied by a thrill is presumptive evidence of aortic stenosis Left ventricular hypertrophy shown by ECG dilatation of the ascending aorta by x ray and an abnormal brachial artery tracing are further confirmation Left heart catheterization is diagnostic if a pressure gradient during systole exists between ventricle and aorta

Fatigue shortness of breath and profuse perspiration were the commonest symptoms Central nervous system manifestations and chest pain were infrequent A systolic thrill and murmur in the aortic area were almost constant These are rarely found in this location in other malformations and are of great diagnostic significance *Differentiation of valvular from infundibular stenosis was impossible*

The indication for surgery in congenital aortic stenosis

(8) Circulation 14 188 199 August 1956

fiber destruction deposition of fibrin like material connective tissue proliferation and eventual scarring and calcification (2) obliterative endangiitis of small vessels and (3) focal predominantly juxtavascular lymphocytic and at times plasma cell infiltration

Angiocardiography in Mitral Disease Preliminary Report The many methods developed for differential diagnosis of mitral stenosis and mitral insufficiency clearly indicate the difficulty of the problem Three sites of injection have been used venous into the left atrium and into the pulmonary artery H Arvidsson and P Ödman[1] (Sodersjukhuset Stockholm) used the last injecting 1 2 1 5 ml/kg body weight of iodopyracet or acetrizoate by an automatic pressure syringe through a cardiac catheter the tip of which lay in the pulmonary artery A two plane film changer was used exposing 6 pairs of pictures/second and recorded simultaneously with the ECG General anesthesia should be used to standardize conditions

In mitral disease pathologic changes occur in the pulmonary arteries Central arteries are wider than normal and in extreme pulmonary hypertension the pulmonary trunk is aneurysmal At the level of the first division of the pulmonary arteries the lumen suddenly becomes narrower than normal Vessels in the peripheral parts of the lung are tortuous and the number of peripheral arteries is diminished particularly at the lung bases which appear almost nonvascular In most cases the central pulmonary veins are widened in proportion to the pulmonary venous capillary pressure When this pressure is high the veins are usually tortuous with sudden caliber changes similar to those of the arteries

In active pulmonary hypertension the increased load on the right heart is manifest by dilatation and hypertrophy of the right ventricle causing backward displacement and rotation of the left ventricle

In 14 cases of uncomplicated mitral stenosis the left atrium was dilated but the degree of dilatation could not be correlated with the pulmonary artery pressure or the pulmonary venous capillary pressure There was always a significant amount of residual blood in the atrium during its maximal contraction

(1) A t ad L 47 97 118 F b ry 1957

failure occurred in 10 and terminated fatally in all Electrocardiograms showed prolonged P R intervals in 5 delayed intraventricular conduction in 6 and left ventricular hypertrophy in 14 Chest x rays showed aorta dilatation in none

Autopsy showed rheumatoid arthritis in 9 patients chronic uveitis in the 4 with ocular involvement unilateral phthisis bulbi in 1 old keratitis in 1 and secondary amyloidosis in 3

The cardiac lesions were strikingly similar to those seen in syphilitic heart disease with aortic regurgitation The aortic valves were dilated and the cusps stretched with varying degrees of fibrosis thickening retraction and rolling of the free margins The commissures were typically separated The aortitis was characterized grossly by discrete intimal plaques centered about each valve commissure and blended with the valvular lesions

Histologically the aortitis seemed active in 5 patients with irregular focal destruction of the media necrosis of muscle fibers fragmentation of elastic lamellae and ingrowth of vascular granulation tissue containing lymphocytes small mononuclear cells and neutrophils The most striking change was fibromuscular thickening of the vasa vasorum with complete obliteration of the lumens in some

The features common to rheumatoid aortitis syphilitic aortitis and rheumatic heart disease with aortic insufficiency are (1) a predilection for men (2) focal destruction of elastic tissue in the aortic ring leading to dilation (3) aortic cusp scarring with retraction rolling of the free margins and focal calcification (4) aortic regurgitation (5) tendency to remain well compensated for years but to fail rapidly once decompensation was begun and (6) occasional coronary insufficiency with angina pectoris as the result of involvement of the coronary ostia

That cardiac aortitis is a systemic manifestation of rheumatoid disease is suggested by the temporal relation between onset of cardiac signs and periods of increased clinical activity of the arthritis absence of clinical or anatomic evidence of syphilis or rheumatic fever and the basic resemblance of the aortic and cardiac lesions to those of other rheumatoid lesions The tissue changes are (1) focal necrobiosis associated with varying degrees of collagen and elastic

lated mitral stenosis coexisting severe tricuspid stenosis was present These patients had tricuspid commissurotomy at the same operation

Aortic stenosis is approached by the ascending aorta which is incised and a pouch of pericardium is sutured to the incision The ungloved finger is inserted into this pouch and the commissures may be split by digital pressure alone in 40 50% of cases A cutting or dilating instrument is other wise required Mortality is still high 15% but significantly less than with the transventricular approach Operations on all 3 valves mitral aortic and tricuspid can be performed through the same right anterior thoracic incision

Mitral regurgitation is dramatically abolished or improved by a new technic in which a mattress suture is passed across the incompetent pole of the valve piercing the annulus fibro sus with a second suture slightly posterior to the first When these are tied down the basal attachments in this portion of the valve are brought closer together and the free margins of the valve can coapt during systole This technic will prob ably prove as satisfactory for previously intractable mitral regurgitation as commissurotomy has for mitral stenosis

Aortic aneurysms can be replaced by homografts from an other person Dissecting aneurysm is a different condition and is treated by opening the outer lumen milking out the clotted blood and re establishing a communication within the aorta

In 5 20% of all myocardial infarctions an aneurysm forms in the ventricular wall The result is a mechanical handicap during systole and diastole Life expectancy is only 3 years compared with 12 in the usual patient after myocardial in farction In 3 such patients the aneurysm has been excised and the myocardial wall resutured with marked sympto matic improvement

Effect of Mitral Commissurotomy on Coexisting Aortic Valve Lesions Joseph F Uricchio and William Likoff[3] (Hahnemann Med College) report 3 patients in whom mitral commissurotomy was succeeded by unmistakable ex aggeration in severity of the aortic valve defect ending in death Dyspnea and edema returned auscultatory signs of aortic valve disease were intensified and the left ventricle

3) New Engl J Med. 256 199 204 J 31 1957

In 4 cases of predominant mitral insufficiency the pulmo nary arteries were normal or only slightly dilated centrally but changes in pulmonary veins were clearly visible The left atrium was dilated in each and in 1 case with atrial fibrillation it was extremely large In none was a regurgi tant jet visualized through the atrioventricular ostium The left atrium rapidly opacified and the cyclic volume variations were considerably greater among these cases than in those with stenosis

In some cases complicating aortic stenosis may be diag nosed In 1 patient the aortic valves were rigid and a narrow jet of blood could be seen in the opacified ascending aorta during ventricular systole In a patient with aortic insuffi ciency thoracic aortography showed regurgitation of con trast solution to the left ventricle

Angiocardiography involves certain risks and should be used only if the desired information will be valuable In pure mitral stenosis with typical physical findings and a normal sized or slightly enlarged heart it probably is not indicated In less well defined cases with atypical clinical findings or those in which conventional chest films show an enlarged ventricular portion of the heart it may be indicated Unsus pected mitral insufficiency may thus be revealed and a dan gerous commissurotomy avoided

Recent Significant Developments in Intracardiac Surgery are reviewed by Charles P Bailey[7] (Hahnemann Med Col lege) *Operations for mitral stenosis are technically* better and results markedly improved when the approach is from the right side rather than the left Using the right anterolat eral approach the interatrial sulcus is dissected and the in ner wall of the left atrium entered Of 196 cases in which the right sided approach was used only 5 had valves in which both commissures could not be opened Success was obtained in 97 3% of cases compared with 33% when the left sided approach was used Valve openings ranged 33 200% larger than those usually obtained from the left A lower incidence of recurrent stenosis and a higher rate of clinical improve ment were achieved

In the right sided approach the right auricular appendage is routinely examined In 10% of patients with clinically iso

( ) P tg ad. M d 0 103 117 A g t 1956

approached through the anterior wall than in those in whom the posterolateral approach was used Thus the syndrome is not restricted to patients who have had rheumatic fever

If the postcommissurotomy syndrome were a reactivation of rheumatic fever it would indicate that direct surgical trauma to the heart can exacerbate the rheumatic process There is no evidence to support this concept The beneficial effect of salicylates in large doses is not diagnostic of rheumatic fever A uniformly favorable response to salicylates does not occur and even if it did such response would not constitute evidence for rheumatic etiology

Recurrent episodes of fibrinous pericarditis without large effusions occur in idiopathic pericarditis and in the postmyocardial infarction syndrome as well as in rheumatic fever Its occurrence is of no value in establishing a rheumatic etiology Prolongation of the P R interval has occurred occasionally but this in itself is not diagnostic

The evidence that the syndrome is not caused by recurrent rheumatic fever is mounting Antecedent streptococcic infections have been demonstrated rarely The antistreptolysin O titer has risen in a few cases Penicillin chemoprophylaxis has failed to prevent the syndrome and its incidence character intensity and duration have been unaffected No correlation was found between the syndrome and the presence of Aschoff bodies in auricular appendage biopsy specimens taken at commissurotomy

No relation to re stenosis has been found and it is believed it occurs irrespective of rheumatic activity The syndrome has been recognized in the postoperative state in patients with pulmonary stenosis interatrial septal defect and other congenital heart disease and has occurred after myocardial infarction in patients without rheumatic fever

The pathology of the pneumonitis in the postcommissurotomy and postmyocardial infarction syndromes is unknown but it may fit into the same category as atypical pulmonary inflammatory reactions due to the development of isoallergic immune bodies to altered tissues in certain persons

Postcardiotomy Syndrome in Patients with Rheumatic Heart Disease Cortisone as Prophylactic and Therapeutic Agent A complication with low mortality but nonetheless

became significantly enlarged because the dynamic effects of uncorrected aortic valve disease were exaggerated following successful mitral commissurotomy

The height of the pressure gradient between the left ventricle and the aorta depends on the degree of stenosis and the rate of blood flow across the opening and the flow is related to the square root of the pressure Muscle contractile strength improves as the diastolic length of the fibers increases but only to a certain critical limit If mitral commissurotomy improves the rate of flow/unit time into the left ventricle the flow is more rapid across the aortic valve In the presence of aortic stenosis this induces a proportional rise in the pressure gradient and the left ventricle can provide higher systolic pressures because the muscle fibers have greater diastolic length due to improved chamber filling In time this leads to concentric left ventricular hypertrophy the muscle fibers overstretch and signs and symptoms of progressive left sided heart failure develop When the aortic valve is incompetent as well as stenotic failure is most apt to ensue

Left sided cardiac catheterization reduces the chance of missing significant aortic valve lesions and may be done in the operating room immediately before and after mitral commissurotomy A significant increase in gradient across the aortic valve after mitral valve obstruction is relieved is important evidence of dynamic aortic stenosis and suggests the need for concomitant aortic commissurotomy

Is Postcommissurotomy Syndrome of Rheumatic Origin? Soon after mitral commissurotomy became a frequent procedure a clinical syndrome was recognized characterized by recurrent febrile episodes associated with pleuritis pericarditis pneumonitis and occasional joint pains In the past this was regarded as reactivated rheumatic fever Samuel Epstein[4] (Maimonides Hosp Brooklyn) re examined the available evidence from clinical physiologic serologic and pathologic studies

The same syndrome has been observed in patients after surgery for pulmonary stenosis and after incision of the pericardium for congenital and arteriosclerotic heart disease It has been seen oftener in patients in whom the heart was

(4) A M A A ch I t Med. 99 253 59 Febru ry 1957

Increased Blood Cell Agglutination Following Ingestion of Fat Factor Contributing to Cardiac Ischemia Coronary Insufficiency and Anginal Pain Contribution to Biophysics of Disease Arthur V Williams A Curtis Higginbotham and Melvin H Knisely[6] (Med College of South Carolina) present evidence that ingested fat can contribute to reduc tion of coronary blood flow by an acute effect an immediate altering of the physical consistency of the blood by red cell agglutination which causes the blood to become more re sistant to passage through the narrowest vessels This is in addition to the well known slowly developing atheroscle rotic narrowing of coronary arteries

In patients with a history of angina microscopic studies of the circulating blood and vessel walls in the bulbar con junctiva were made in the fasting state and after a high fat meal Of 10 patients tested 8 had a conspicuous increase in the degree of agglutination of the circulating blood follow ing the fat enriched meal Three who responded with maxi mal agglutination of the blood also had visibly plugged bul bar conjunctival vessels and later developed anginal pain No patient developed anginal pain unless increased intra vascular agglutination of the blood and plugging of some visible conjunctival vessels had occurred Some healthy medical students but not all developed a microscopically detectable mild agglutination of the blood following inges tion of fat

The observations show a definite relation between inges tion of fat agglutination of blood stoppage of the blood flow in bulbar conjunctival vessels and in patients with the most severe agglutination development of angina These coincide with the peak of the dietary lipemia reported by others The observations suggest a possible mechanism for de creased volume of blood flow through the myocardium re sulting in myocardial ischemia and anginal pain Such a mechanism might explain the sharp rise in thromboembolic phenomena in Scandinavian countries following World War

(6) A g 1 gy 8 29-40 F bruary 1957

capable of increasing morbidity delaying convalescence increasing duration of hospitalization and frequently incapacitating the patient at variable periods after surgery has been observed following cardiotomy It occurs most commonly after mitral commissurotomy but also follows pericardiotomy It was seen by David T Dresdale Charles B Ripstein Santiago V Guzman and Murray A Greene[5] (New York) in a patient in whom only cardiotomy was performed because of technical difficulties The syndrome is characterized by the following clinical features in descending frequency fever chest pain of a pleuropericardial nature congestive heart failure pleural effusion polyarthritis arrhythmia abdominal pain and subcutaneous nodules A few instances of hemoptysis and psychosis have been reported Laboratory evidence for a nonspecific inflammatory process is frequently present Most initial episodes occur within a month after surgery *Death has occurred infrequently*

Cortisone was found to have a definitive suppressive effect on the syndrome The syndrome was noted within 3-8 weeks after surgery in 8 (31%) of 26 patients not receiving cortisone immediately after operation and in 4 (7%) of 58 who received cortisone postoperatively The incidence was similar in both groups—occurring within 3 24 weeks in 8 (31%) of the 26 and 17 (29%) of the 58 patients—when cortisone was discontinued The immediate postoperative course of patients who received cortisone prophylactically was less stormy than that of those who did not As a therapeutic agent cortisone was superior to salicylates Pyramidon® and antibiotics that did not favorably affect the clinical manifestations of the syndrome Cortisone in doses of 50 300 mg daily depending on the individual caused dramatic remission of symptoms and fever in the syndrome It is recommended that ACTH be given prophylactically for 2 days preoperatively and for 8 10 days postoperatively in patients undergoing rheumatic mitral valvuloplasty

(5) Am J Med 21 57 74 J ly 19 6

ATHEROSCLEROSIS AND CORONARY DISEASE

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II when the amount of fat available increased sharply and might explain the more frequent angina and myocardial infarction in patients placed on high fat diets for peptic ulcers They also suggest a common cause for nocturnal angina following a fat laden evening meal angina at rest and an apparent decrease in exercise tolerance in some cardiac patients following fatty meals

Effect of Heparin on Lipemia Induced Angina Pectoris Slow intravenous injection of 15 20 ml of 10% sesame oil emulsion produces a drop in oxygen tension and decreases the amplitude of myocardial contraction in dogs whose left coronary arteries have been ligated Postprandial lipemia may induce attacks of angina pectoris in patients with severe coronary artery disease and intravenous injections of small doses of heparin sodium quickly clear the turbidity of lipemic plasma and abolish alimentary lipemia

Peter T Kuo and Claude R Joyner Jr[7] (Univ of Pennsylvania) studied 7 patients with severe coronary heart disease old myocardial infarction and angina pectoris in whom lipemia was induced by fatty meals of heavy cream In this way 19 acute anginal attacks were induced after latent periods ranging from 5 to 5½ hours Within 15 minutes after onset of pain the patient received an intravenous injection of either sodium chloride or 5 25 mg heparin

Sodium chloride afforded no subjective relief in any of the 4 patients in whom it was used and had to be followed by an intravenous injection of heparin to terminate the attack Heparin induced subjective relief within 10 minutes in 14 of the 15 to whom it was given Glyceryl trinitrate gave prompt subjective relief in 4 others in whom attacks were similarly induced Objective evidence of improvement was seen in ballistocardiograms electrocardiograms and pneumograms Heparin abated the postprandial lipemia as measured by turbidity of the plasma concentration of neutral fat in the serum and paper electrophoretic lipoprotein patterns

These studies suggest that efforts should be made to minimize postprandial lipemia in patients with severe coronary artery disease and angina pectoris Dietary fat restriction with or without administration of an antilipemic agent should be considered in therapy

(7) J A M A 163 727 731 Mar 2 1957

Diet and Development of Coronary Heart Disease Coronary or ischemic heart disease results from inadequate blood supply to the myocardium caused by atherosclerosis or coronary thrombosis Control of atherogenesis is the major problem in prevention or control of such heart disease With age and heredity as limiting factors the mode of life in most persons determines whether extensive and irreparable changes in the coronary arteries come early or late Ancel Keys[8] (Univ of Minnesota) correlated human and animal experiments biochemical theory clinical observations and epidemiologic studies

Measurement of cholesterol and cholesterol bearing lipoprotein is not diagnostic and has slight prognostic value for individuals but does show statistically significant differences between groups No one of the possible measurements in the cholesterol lipoprotein system is superior to another including ultracentrifuge determinations all can be correlated with one another and with the tendency toward atherosclerosis Whenever a population has a relatively high serum cholesterol average (over 220 mg /100 ml) for its clinically healthy members incidence of coronary heart disease is high

Obesity per se is not well correlated with incidence of ischemic heart disease and there is only a slight relation between relative obesity and serum cholesterol concentration within specific socioeconomic and age groups Experiments on man in calorie balance show that marked changes in proportion of total calories provided by fats quickly produce statistically significant changes in total cholesterol and β-lipoprotein cholesterol concentrations and maintain them for the duration of the new diet In general the relative prevalence of ischemic heart disease in various countries tends to correlate directly with the average proportion of dietary calories supplied by fats

All fats are not equivalent in their effects on the cholesterol lipoprotein system and atherogenesis There is a rough but imperfect relation between the cholesterogenic effect of different food fats and the degree of saturation of their constituent fatty acids Phytosterols occur in many foods of plant origin and are available commercially but

(8) J Chron Dis. 4 364 380 October 1956.

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even the most enthusiastic proponents claim only moderate reductions in serum cholesterol concentrations and 10 Gm or more of the most effective phytosterols is required to achieve this Similar conclusions apply to lecithin and other substances occurring in natural foods and so eagerly promoted by some commercial interests

A low fat diet influences serum cholesterol and lipoprotein levels of the coronary patient as it does in the normal person Such a regimen may retard progression of atherogenesis although the clinical status may be unimproved Maintenance on a low fat restricted calorie regimen is associated with improved prognosis in patients with angina pectoris or myocardial infarctions Serum cholesterol or other elements in the lipoprotein system must be measured periodically to evaluate efficacy of the regimen

Modification of Abnormal Serum Lipid Patterns in Atherosclerosis by Administration of Sitosterol is reported by Maurice M Best and Charles H Duncan[9] (Univ of Louisville) Phytosterols closely related to cholesterol are present in higher plants The most widely distributed are the sitosterols of which there are at least 5 types *Gamma sitosterol* is the principal sterol of soybean oil and presumably the active component of the sterol mixture which inhibits absorption of cholesterol in experimental animals Sitosterol is relatively nonabsorbable from the intestinal tract

Sitosterol was administered to 24 patients as a 20% suspension predominantly beta type 6 8 Gm orally immediately before ingestion of food usually totaling 18 25 Gm/day Diet was unrestricted Patients had a variety of diseases including coronary and peripheral arterial disease hypothyroidism familial hyperlipemia with xanthomatosis and hypercholesteremia secondary to renal disease The largest group was 11 patients with prior myocardial infarction

During sitosterol administration mean reduction of serum cholesterol was 15 5% of phospholipid 9 4% and of total lipid 13 8% Patients with myxedema showed greatest reduction Fluctuations during control and treatment periods in patients with familial hyperlipemia were so great that results of treatment could not be evaluated Observations to date are insufficient for conclusions regarding the effect of

(9) \ n I t Med 45 614 6 O t be 1956

sitosterol on atherosclerosis and further study is needed There have been no recurrent infarctions in this group and no toxic effects attributable to sitosterol

Effect of Beta Sitosterol on Serum Lipids of Young Men with Arteriosclerotic Heart Disease was investigated by John W Farquhar Ralph E Smith and Mary E Dempsey[1] (Univ of Minnesota) in 15 men aged 26-45 years who had sustained previous well documented myocardial infarction whose blood pressures were normal and who had no diabetes

The study was in three phases 6 12 weeks before medica tion sitosterol for 12 24 weeks and placebo administration for the following 10 16 weeks Diets were constant and in cluded 23 28% fat calories in 9 and 40 48% in 6 patients Cho lesterol intake was 200 300 mg /day in the fat restricted diets and 900 1 000 mg /day in the unrestricted Three equal portions of beta sitosterol were given orally immedi ately before meals totaling 12 18 Gm /day Serum was ob tained in the fasting state at weekly or biweekly intervals

When the baseline serum lipid values of the 15 patients were matched with those in a comparable group of 15 nor mal subjects without heart disease the abnormal group was characterized by significantly increased cholesterol beta lip oprotein lipid and total lipid In the group as a whole beta sitosterol significantly reduced average serum cholesterol and beta lipoprotein lipid slightly reduced total lipid and slightly increased alpha lipoprotein lipid However when individual responses were analyzed results were not con sistent or uniform Several patients whose serum cholesterol was well above normal showed decreases of only 10 30 mg / 100 ml Beta lipoprotein changed only slightly in 3 and even increased in 1 patient taking beta sitosterol The apparent lack of deleterious effects coupled with the observed changes suggests potential benefits of sitosterol administration Its therapeutic role in clinical medicine has not yet been established

Practical Method for Reduction of Plasma Cholesterol in Man is described by Henry A Schroeder[2] (Washington Univ) Unproved experimental evidence indicates that

(1) C lat 14 77 82 J ly 1956
( ) J Ch c D 4 461-468 N embe 1956

trace metals pyridoxal phosphate and unsaturated fatty acids may be interrelated in production of atherosclerotic lesions or in synthesis of cholesterol and fatty acids Calcium disodium ethylenediamine tetra acetate a nonmetabolized chelating agent dramatically lowers plasma cholesterol in man when given intravenously Certain vegetable oils with high iodine numbers lower plasma cholesterol in man even when given as the major source of calories other vegetable oils and saturated animal fats act oppositely

A diet which avoided dairy products and hydrogenated vegetable oils (both containing saturated fatty acids) excess animal fat on meat and meat products and which excluded pork entirely was given to 20 ambulatory patients Fish was allowed ad lib The caloric equivalent in fat was thus reduced from the usual 40% to less than 20% This diet by itself did not affect plasma cholesterol significantly

Adequate intake of vegetable fat containing linolenic acid was provided by using soybean or corn oil for cooking and salad dressings Other sources of linolenate are linseed millet seed walnut and beechnut oils An attempt was made to provide 0.2-0 5 Gm linolenic acid daily Calcium disodium ethylenediamine tetra acetate 1 Gm /day orally and pyridoxine hydrochloride 10 mg /day orally were added With this regimen mean cholesterol concentrations fell 29% in 2 months but were only 20% lower after 4 months than the initial mean value of 258 mg /100 ml In 9 patients plasma cholesterol concentrations reached levels comparable to the Oriental normal In 3 changes were insignificant

No adverse symptoms appeared Frequency of anginal attacks in 5 patients was claimed by them to be less No changes were noted by 2 patients who previously had progressive intermittent claudication

The regimen apparently offers a simple practical and not too restrictive diet for ambulatory patients taking most meals at home It is almost impossible if the patient eats in restaurants The 9 patients achieving the lowest cholesterol values were the most careful in their diets The diet without chelating agent or vitamin B_6 usually did not produce profound falls in plasma cholesterol

► [Only a few years ago it was thought that atheroma was a progressive and hopeless disorder and that no means of treatment was available Now the situation is reversed and there are so many recommended methods of

treatment that the doctor finds himself at a loss as to which ones to use Among the dietary methods which have been advocated are total caloric restriction solid fat restriction reduction in intake of saturated fatty acids etc Evidence is increasing that while all these may be important restriction of total fats and of saturated fatty acid is probably the most important In addition to dietary methods there is strong evidence that three different types of drugs may be of value These include sitosterol heparin and chelating agents Heparin appears to have a distinct advantage over Dicumarol® in that its dosage is easier to regulate and that it not only has an anticoagulant effect but an antilipemic effect On the other hand it has to be injected and is expensive Possibly the ultimate answer will come from both qualitative and quantitative restriction of fat the use of one of the less expensive antilipemic agents and possibly also the long range use of oral anticoagulants The apparent confusion in relation to this subject existing at present is a healthy sign because it indicates that progress is being made more rapidly than final evaluation can be achieved —Ed.]

Correlations in Coronary Arterial Disease were made by Jesse E Edwards[3] (Mayo Clinic) in a review of autopsies on patients dying at home while under the care of a physician or in the hospital and autopsies done at the request of the coroner's office The highest incidence of significant coronary arterial narrowing occluding more than half the lumen was found in ages 50 59 About 75% of men in this age group had such lesions Significant coronary atherosclerosis is common but the clinical and pathologic manifestations are diverse

Many patients with significant coronary atherosclerosis at autopsy either had no history of cardiac disease or had angina pectoris without a history of myocardial infarction The myocardium in these patients may have no lesions or may show a healed infarction appearing as so called focal fibrosis Only a few patients who die suddenly of coronary disease have coronary thrombosis or other acute occlusion Usually there is severe atherosclerosis at one or many foci in the coronary arteries without acute myocardial infarction The cause of sudden death in these patients is generally conceded to be myocardial ischemia which leads to serious arrhythmias such as cardiac standstill or ventricular fibrillation

Patients with severe coronary atherosclerosis may have angina decubitus continuous angina even at rest in bed which may be so severe and prolonged that acute myocardial infarction is suspected If such patients die pathologic examination may reveal no infarction In some cases such

(3) B ll N w Y k A d M d 33 199 217 M b 1957

patients may have coronary insufficiency without infarction

Since 85% of patients survive the acute myocardial infarction pathologists see only selected patients with acute infarction Transmural infarction was about twice as frequent as subendocardial infarction The major types of death were myocardial failure coronary failure and rupture of the heart less commonly shock and thromboembolic complications Factors which influenced the occurrence of myocardial failure were a previous infarct and an acute transmural infarct The designation coronary failure was applied to patients who while convalescing from acute myocardial infarction had episodes of recurring pain indistinguishable from those of a new myocardial infarct Most died suddenly without pulmonary edema The attacks of pain seem to represent ischemia of the noninfarcted myocardium and the sudden death may result from a serious arrhythmia originating in the viable ischemic myocardium

Of 133 patients studied 15% died of rupture of the heart In each the acute infarct was transmural and *in an area not* affected before There was no evidence that anticoagulants favored rupture It commonly occurred before the 5th day and in some so soon after infarction that it could not be identified on gross examination Histologic examination gave the earliest evidence of infarction showing it to be 12 18 hours old when the rupture occurred The rupture is not simply a blowout of the wall but seems to have a shearing action which initially causes a tear at the endocardium in the peripheral portion of the infarct or at the junction with bordering noninfarcted muscle Blood from the left cavity then dissects through the muscle into the epicardium through the epicardium and into the pericardial sac An uncommon type is rupture of a papillary muscle usually the posterior causing mitral insufficiency

Thromboembolic complications which would contribute to death were observed in 8 of the 133 patients none of whom received anticoagulants In another group 210 patients with acute myocardial infarction pulmonary embolism occurred in 16% it was massive in 6% and either caused or significantly contributed to death

Of 250 patients who showed scars of an old myocardial infarction at autopsy less than half had clinical evidence of it

In those who died of cardiac causes causes of death were congestive heart failure without acute infarction recurrent acute myocardial infarction pulmonary embolism occurred without congestive heart failure or acute infarction was the most common type of cardiac death in patients with healed myocardial infarction In all patients with coronary disease including those with healed myocardial infarction the exist ing coronary disease may be a basis for acute myocardial ischemia and sudden death as in patients with coronary disease without myocardial infarction

In the discussion William Dock stated that evidence indi cates that motion or violent struggling does not have any thing to do with rupture In 2 series of patients in which al ternate patients were kept in bed or allowed to sit up for meals and use a commode after they were no longer in shock the death rate was twice as high in the group kept in bed

Clarence E de la Chapelle stated that in many patients with heart failure associated with hypertension underlying atherosclerosis of the coronary arteries cannot be demon strated At autopsy such patients may show little or no coro nary disease and the myocardium although markedly hy pertrophied will appear grossly normal In such hearts the coronary arterial system obviously is inadequate for the hy pertrophied muscle mass and slight abnormalities precipi tate myocardial failure

Careful histologic examination of multiple sections taken from the hearts of persons dying suddenly without evidence of gross infarction often reveal changes indicative of ische mia of muscle fibers or muscle bundles In most of these cases death occurred within 6 12 hours of clinical onset Chemical methods may show changes in these muscle fibers or bundles which cannot be seen histologically

Myocardial Infarction Epidemiologic and Prognostic Study of Patients from 5 Departments of Internal Medicine in Oslo 1935 1949 is presented by Knut Westlund and Anna Hougen[4] (Oslo) The study included 1 613 patients of whom 684 died during their initial hospitalization Of 929 patients discharged alive and followed 621 died Date of death was known in all cases and the death certificate was located in all but 16 Autopsy results were obtained in 208 of these patients

(4) Act m d. sca d 1 154 pp 315 1956

During the war incidence of myocardial infarction among men dropped considerably particularly at ages under 60 After the war a large increase occurred in men of all ages Among women no such reduction was seen during the war and the postwar increase was moderate and limited to ages over 60 At all ages under 80 incidence of myocardial infarction was greater in men than women Incidence in women corresponded to incidence in men on the average 10 years younger The occupational distribution of men showed a higher proportion of executive employees and considerably fewer workers than expected on the distribution of population in Norwegian urban areas

The mortality ratio (ratio between actual and expected number of deaths) depended on the age at discharge and the number of years after discharge Mortality in the first year after discharge among men aged 40-49 was 15 5 times the expected mortality in the general population At ages 80-89 it was 4 8 times the expected mortality Among men 60 69 the mortality ratio varied from 8 1 in the first year after discharge to 2 1 in the tenth year and over Absolute mortality increased steadily with age During the war years mortality during the first year after discharge was as high or higher than in other years but was distinctly lower in the following years compared to mortality during nonwar years

The mortality ratio was greater for patients with a previous myocardial infarction than for patients without Patients who had been seeing a doctor for pains or sensations in the heart region had a poorer prognosis than patients with such symptoms who had not consulted a doctor Patients without hypertension had a considerably lower mortality ratio Pains in the heart region at discharge or signs of heart failure indicated a poor prognosis Occupational group type of infarction pain and duration from beginning of infarction pain until admission had no effect on the mortality ratio

Study of C Reactive Protein in Serums of Patients with Acute Myocardial Infarction In classic cases the history physical findings ECG changes and alteration in sedimentation rate clearly indicate the diagnosis However in states of coronary insufficiency in which lesser degrees of myocardial necrosis supervene the diagnosis is often not apparent

and other diagnostic aids are sought According to Ernest L Levinger Hyman Levy and Samuel K Elster[5] (Mount Sinai Hosp New York) C reactive protein determination is a promising new aid

C reactive protein is an abnormal protein absent from the blood of normal patients which appears as an acute phase response in various clinical conditions such as inflammation neoplasia and granuloma formation C reactive protein was determined in 62 patients hospitalized within 24 hours of onset of acute chest pain Of 50 with proved myocardial infarction C reactive protein appeared in the blood of 49 and in amounts which correlated roughly with other laboratory indexes of myocardial infarction Patients who had moderate or larger amounts had as a group more prominent fever leukocytosis and elevated sedimentation rates although no correlation was evident in a single blood sample between its C reactive protein content and other abnormal blood tests The amount and duration of C reactive protein were independent of the particular ECG pattern of myocardial infarction

In 15 patients C reactive protein appeared before ECG changes in 25 both became abnormal coincidentally and in 3 ECG changes preceded the appearance of C reactive protein

In the 12 patients with severe chest pain of coronary origin who apparently had no infarction C reactive protein was absent from all blood specimens taken serially A single blood specimen that fails to contain C reactive protein does not eliminate the diagnosis of myocardial necrosis since C reactive protein may not appear in the blood until 48 hours after an acute myocardial infarction

The C reactive protein test is suggested as an additional useful and sensitive laboratory aid in diagnosis of myocardial infarction One limitation is its lack of specificity C reactive protein has been reported in the blood of patients with congestive heart failure

Anticoagulant Therapy of Acute Myocardial Infarction Evaluation from Autopsy Data with Special Reference to Myocardial Rupture and Thromboembolic Complications The benefits of anticoagulants in decreasing the complica

(5) A I t M d. 46 68 78 J a y 1957

tions which commonly follow myocardial infarction are well described *but published data also indicate that myocardial* rupture and fatal hemopericardium are increased after anti coagulant therapy Kyu Taik Lee and Robert M O Neal[6] (Washington Univ) analyzed autopsy records of 108 patients who received anticoagulant therapy 218 who during the same period received no anticoagulants and 174 who died between 1910-1945 before anticoagulants were available All 500 patients had had an acute myocardial infarction

Incidence of thrombi found in the 3 groups of patients was approximately the same and separation of those who re *ceived adequate therapy (prothrombin activity of 30% or* less) from those inadequately treated showed no difference in incidence of thrombi However, no thrombi were found in 52% of patients in whom adequate anticoagulation was started within 3 days of the clinical onset of infarction compared to 41% in the untreated group No significant differences in days of survival were demonstrated among the 3 groups

Incidence of myocardial rupture among the 500 patients was 5% with no significant difference in patients treated before 1945 compared to those treated after 1945 However the incidence among those receiving anticoagulants (12%) was significantly greater than among those not so treated (2 3%) Surprisingly the incidence in the treated group was the same whether or not treatment was adequate Average age of the patient average weight of the heart incidence of healed infarct and incidence of marked luminal narrowing of the coronary arteries were similar in the patients with and without myocardial rupture A recent thrombus occluding a coronary artery was found in 72% of those with rupture and in only 38% of those without A history of hypertension was obtained in 80% of patients with rupture and in only 63% of those without

The average time at which myocardial rupture occurred was the 7th day after clinical onset of infarction The site of rupture was the left ventricle in 21 right ventricle in 3 and interventricular septum in 1 approximating the same ratio at which right and left myocardial infarction occurred In no case was there massive fatal hemopericardium in

(6) Am J M d 1 555 559 October 1956

anticoagulant treated or untreated patients without myocardial rupture

The entire beneficial effect of anticoagulant therapy cannot be evaluated from autopsy data Fatal cases are usually those with the most extensive disease and are most likely to show poor results with any therapy The findings suggest that anticoagulant therapy is not effective in reducing thromboembolic complications of acute myocardial infarction unless therapy is begun within the first 3 days Incidence of myocardial rupture is 5 times greater in anticoagulant treated than untreated patients a highly significant difference and similar to the results of others Possibly the selection of patients receiving anticoagulants accounts for the high incidence of rupture but there was no evidence for this in the clinical histories

Use of Aramine® in Clinical Shock George H Stechel Stanley I Fishman George Schwartz Hyman Turkowitz Peter F Madonia and Arthur Fankhauser[7] (Brooklyn) used Aramine® in 250 cases in which diagnosis was verified and report their results in 42

Of the 42 patients 15 left the hospital alive 27 died Blood pressure did not respond in 6 Norepinephrine was substituted in 12 patients in whom no response was obtained with Aramine® but they subsequently died

With 300 mg Aramine® in 1 000 ml of 5% dextrose in water a rise in blood pressure to adequate levels can be anticipated in 5 minutes Lack of response in 10 minutes usually indicated complete failure In all cases after Aramine® was discontinued blood pressure slowly fell to low levels but resumption of therapy was usually unnecessary because pressure gradually readjusted

Advantages of Aramine® over other pressor agents were relatively easy control of the pressure rapid rise to the desired level and gradual fall in pressure when the drug was stopped There were no deleterious results from infiltration of tissue by infusion fluid containing Aramine®

Particular mention is given the use of Aramine® in shock due to myocardial infarction solely because of current interest in use of vasopressors for this condition No blanket endorsement for the u e of Aramine® or any other vaso

(7) C I t 13 834 836 J 1956

pressor in shock due to myocardial infarction is intended

Differential Diagnosis of Angina Pectoris is reviewed by Joseph E F Riseman[8] (Harvard Med School) Diagnosis rests on the patient s ability to describe his symptoms and the physician s ability to evaluate the patient s description Angina pectoris is not synonymous with coronary artery disease arteriosclerotic heart disease coronary heart dis ease or coronary insufficiency Angina pectoris is only one of the manifestations of coronary artery disease most com monly due to coronary arteriosclerosis Heberden s original description has not been improved They who are afflicted with it are seized while they are walking (more especially if it be up hill and soon after eating) with a painful and most disagreeable sensation in the breast which seems as if it would extinguish life if it were to increase or continue but the moment they stand still all this uneasiness vanishes

Angina develops within seconds and without discomfort between attacks It does not increase gradually over a pe riod of hours Pain is most commonly located under the mid or upper breast bone Discomfort limited to a region under the left breast is suspect Radiation occurs in only about 60% most commonly to the inner aspect of the arm Pain in the outer aspect is more likely due to disease of the cervical spine The discomfort is vague and difficult to describe ex actly painful but not necessarily described as pain—press ing squeezing and choking are terms commonly used At tacks are precipitated by exertion—a helpful point in diagnosis—by emotion cold or after meals and are short Practically all last less than 3 minutes if measured by a stop watch

The patient with angina pectoris usually has all these characteristics of the syndrome If one is absent the patient probably does not have angina and another cause for the symptoms must be sought Physical examination and labo ratory studies are of little value To date no objective test such as the exercise tolerance test has been adequate False negatives and positives are frequent and each carries some danger to the patient

Symptoms resembling angina may result from disease of the brain skeletal system gastrointestinal system or struc tures in the bony thorax or the thoracic cage The most dif

(8) Circulation 14 42 -434 September 1956

ficult differentials are from psychoneurosis and gallbladder disease A careful history resolves the problem in most in stances prolonged observation in others

Completed 25 Year Follow up Study of 456 Patients with Angina Pectoris is presented by David W Richards Edward F Bland and Paul D White[9] (Massachusetts Gen l Hosp) This series originally of 500 patients was reported in 1931 and re evaluated in 1943 All patients had paroxysmal op pression in the front of the chest generally substernal often radiating to the feet or both arms brought on particularly by exertion especially after eating in cold weather or when hurried and relieved in a few minutes by rest or nitrites In the current study 44 patients were excluded because their angina pectoris conceivably resulted from associated disease rather than from atherosclerosis

Of the 456 patients 445 are dead 6 are living and 5 have been lost to follow up Average duration of survival in the 445 patients who died was 9 4 years and the 6 living patients have survived an average of 31 7 years Deaths were due to cardiac causes in 76% Approximately one fifth of the entire group had normal cardiac findings blood pressure and ECG at first examination and these patients as a rule lived longer than the others Hypertension myocardial infarction car diac enlargement and abnormal ECG were more frequent in patients who died early in their disease than in those sur viving longer

When survival in patients with angina pectoris was com pared with expected survival of the unselected United States population it was found that angina pectoris imposes a con tinuous excess mortality load on patients almost constant during the entire period of observation This excess mortal ity is greater in men of whom some 7% die annually in addi tion to the over all expected mortality In women the figure is 5 3% The excess mortality does not differ between young er and older groups These studies indicate a more hopeful outlook for patients with angina pectoris than was formerly recognized

Cardiac Pain from Esophageal Lesions Two cases are re ported by Geoffrey Bourne[1] (St Bartholomew s Hosp Lon don) Esophageal contraction of an abnormal type can pro duce pain mimicking that of cardiac origin Patients

(9) J Ch D 4 423-433 Oct b r 1956
(1) La t 1 89 893 J e 9 1956

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Symptoms resembling angina may result from disease of the brain skeletal system gastrointestinal system or structures in the bony thorax or the thoracic cage The most dif

(8) Circulation 14 4 -434 September 1956

terial oxygen unsaturation was not proportional to the de gree of pain experienced Only 1 patient had polycythemia and it was mild

Two types of chest pain were described One was pro voked by effort of variable duration but usually less than 10 minutes located either substernally or precordially and of variable severity ranging from oppression without true pain to severe pain without oppression it could be experi enced during tachycardia and was relieved by nitroglycerin and by rest The second type was protracted generally but not always provoked by effort not promptly relieved by rest of considerable severity occasionally simulating myocardial infarction and relieved inconstantly by nitroglycerin or by oxygen inhalation

The chest pain probably represents myocardial ischemia of the right ventricle The greatly hypertrophied right ven tricle requires an increased oxygen supply but because of the high intracavity pressure during systole and the pro tracted systole coronary flow to the right ventricle is de creased Intramural pressure is roughly equivalent to the intracavity pressure and intramural perfusion of the right ventricle is probably substantially prohibited during the portion of systole when the right ventricular pressure ex ceeds that in the aorta Another factor is the low cardiac output which cannot be augmented during exercise

Pathologic examination of postmortem specimens in 5 other cases of severe isolated pulmonic stenosis revealed extensive fibrosis of a patchy nature limited to the right and sparing the left ventricle

Application of Induced Bronchial Collateral Circulation to Coronary Arteries by Cardiopneumonopexy II Hemo dynamics and Measurement of Collateral Flow to Myocar dium were investigated by Romeo A Vidone John L Kline Martha Pitel and Averill A Liebow[3] (Yale Univ) When the pulmonary artery in the lung is ligated bronchial col lateral circulation is induced which carries a considerable quantity of blood to the heart if implemented by cardiopneu monopexy The minimal collateral blood flow to the heart has been estimated in various animals to be from 4 1 to 16%

(3) Am J P th 32 897 925 S pt-Oct 1956

frequently summon medical aid diagnosis is often coronary thrombosis and morphine is given In 83 of 332 reported cases there were *long intervals without pain*

When pain clinically attributable to coronary disease is not associated with any other abnormality, clinical ECG or radiologic the esophagus should be fully investigated If a lesion is found proper treatment can be instituted

Man 54 had a sudden attack of pain in the chest at the upper part of the sternum with radiation down the left arm and to the neck Morphine relieved the pain He was not in shock and all findings were normal A similar attack the same day and another 2 days later were relieved by morphine Laboratory findings including ECG were normal

After discharge he remained well for 2 years and was then re admitted as an emergency with severe gripping retrosternal pain *radiating to the left of the thorax He was perspiring* nau eated and in shock No other abnormality was found He had 7 further attacks all lasting an hour or more and all requiring opiates The ECG and the size and shape of the heart were normal Because he was noted to swallow air from time to time the esophagus was sus pected as the site of the lesion A barium swallow was obtained and a diverticulum of the middle third of the esophagus was found

The other case was similar and a sliding hiatus hernia was found

Chest Pain in Patients with Isolated Pulmonic Stenosis Five patients are described by Richard P Lasser and Ga briel Genkins (Mount Sinai Hosp New York) who com plained of substernal and precordial chest pain and were *proved to have congenital stenosis of the pulmonic* valve a normal aortic root and an intact interventricular septum The diagnosis was made by cardiac catheter and was con firmed by surgery

All the patients had right ventricular systolic hyperten sion that equaled surpassed or closely approached the sys temic blood pressure Diastolic pressure in the right ven tricle was moderately elevated in 2 markedly elevated in 1 and normal in 2 The electrocardiogram revealed right ventricular hypertrophy in each Fluoroscopy demonstrated unequivocal right ventricular enlargement in all cases Post stenotic dilatation of the main pulmonary artery was mod erate in 3 *minimal in 1 and absent in 1 Postoperatively* these vessels appeared the same although the pain had been relieved The presence absence or degree of peripheral ar

(2) Circulation 15 258-266 February 1957

vessels which are transmitted to the brain as vasodepressor reflexes These drugs are effective in the supine position the degree of blood pressure reduction almost equaling that observed in the upright position If the response to reserpine is inadequate it is often desirable to use a ganglionic blocking agent or an adrenergic blocking agent also These drugs act peripherally the reduction in blood pressure is primarily in the orthostatic position and it may become necessary to elevate the head of the bed to induce the maximum response

Cerebral function is improved by lowering the blood pressure in hypertensive patients particularly if there is hypertensive encephalopathy If pressure is reduced excessively cerebral blood flow may decrease sharply Syncope may result when the patient stands Improvement in intractable angina pectoris suggests that the ratio of coronary blood flow to metabolic demand is improved by lowering the pressure and generally cardiac failure is improved Hydralazine by increasing the heart rate and cardiac output may produce palpitation angina and even myocardial infarction

Glomerular filtration rate and renal blood flow are reduced slightly when the blood pressure is reduced acutely except that hydralazine temporarily increases renal blood flow without affecting the glomerular filtration rate Renal function is depressed more with ganglionic blocking agents than with the centrally acting agents In patients with severe renal disease and hypertension blood pressure reduction must be done cautiously Even small reductions in glomerular filtration may produce renal decompensation

In a hypertensive emergency the state of renal compensation should be estimated by the blood urea nitrogen If normal the disturbed sensorium cannot be attributed to renal factors Retinal hemorrhages suggest the degree of general arteriolar damage Papilledema suggests increased intracranial pressure and cerebral edema which accounts for deranged cerebral function if renal function is normal

After the state of renal function is known therapy should be approached systematically If immediate blood pressure reduction is not mandatory parenteral reserpine or rescinnamine is the drug of choice 2 5 mg repeated in 2 hours if reduction in pressure is not adequate When a maximum dose of 10 mg reserpine or 15 mg rescinnamine every 6 hours is inadequate a ganglionic blocking agent should be tried

of total inflow into the coronary sinus even in the absence of demonstrable myocardial ischemia

Dye curves and angiocardiography demonstrate rapid passage of blood from the aorta through the collateral system long before there has been recirculation When pressure in the vessels of the lung exceeds that in the coronary arteries a relatively large flow may occur from the pulmonary arteries toward the heart after simple cardiopneumonopexy

These observations demonstrate that with cardiopneumonopexy of a lung and a ligated pulmonary artery there is a measurable collateral inflow of blood to the myocardium The connections are of precapillary size and occur only with coronary arteries and never directly with the veins thus the collateral blood flow must have the same capillary distribution as any blood reaching the distal coronary arteries Larger collateral flows were observed in dogs whose coronary arteries had been wrapped in irritating polyethylene at their sources

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HYPERTENSION

Treatment of Hypertensive Emergencies Marked and sudden elevation in blood pressure itself regardless of cause may become a direct threat to the patient s life and its control may be lifesaving The more important complications associated with sudden elevations of pressure are hypertensive encephalopathy malignant hypertensive crisis fulminating heart failure secondary to severe hypertension and cerebral hemorrhage or coronary insufficiency secondary to a sudden and severe rise in blood pressure

John H Moyer[4] (Baylor Univ) presents a general approach to the treatment of hypertensive emergencies Rauwolfia hydralazine and veratrum act centrally to depress vasoconstrictor impulses traveling from the brain to the blood vessels Hydralazine and rauwolfia act directly whereas veratrum acts directly as well as reflexly by stimulating afferent impulses originating in the heart and great

(4) GP 15 105 132 M rch 1957

After it has been decided to use a hypotensive drug therapy should begin at the first indication of advancing cardiovascular disease—it is the vascular disease that kills—and this can be identified by testing renal function heart size and eyegrounds and by electrocardiograms

Hypotensive drugs can reverse malignant hypertension if treated before renal function becomes too low In milder forms the pressure should be lowered enough to slow the advance of vascular disease Blood pressure by itself may not be the criterion and in most patients merely lowering the diastolic pressure 10 mm Hg probably is of no appreciable benefit

With the use of hexamethonium irregular absorption is a big problem and occasional faintness may result Mecamylamine hydrochloride is readily absorbed and apparently this difficulty is avoided Pressure is not apt to be lowered much in the supine position Raising the head of the bed has not helped much In time most patients become refractory to the drugs which must then be changed or temporarily stopped

If reserpine has proved effective it may also be combined with a ganglion blocking agent Apresoline® is effective in some patients Hypertensive encephalopathy is simply and dramatically treated with sodium nitroprusside

Progress has been made in the control of hypertension and is continuing In some cases the drugs fail because there is no response the response is only transient the patient does not take the drug or the side effects are too disabling

Mecamylamine New Orally Effective Hypotensive Agent Experimental and Clinical Evaluation According to Edward D Freis and Ilse M Wilson[6] (Georgetown Univ) mecamylamine (3 methylaminoisocamphane) hydrochloride a secondary amine causes marked and prolonged reduction in blood pressure and ganglionic blockade It is well absorbed from the gastrointestinal tract

A single intravenous dose of 15 20 mg and in the same patient the next day a single oral dose of 10 15 mg significantly reduced supine blood pressure and induced noticeable postural hypotension After intravenous administration blood pressure gradually fell to minimum values in ½ 1 hour and returned to control values in 6-12 hours After oral dos

(6) A M A. Arch I t. Med. 97 551 561 M y 1956

There is little difference in responsiveness among the various ganglionic blocking agents Hexamethonium is preferred for initial therapy because of its quicker action but if it is inadequate a continuous infusion of Arfonad® is probably the therapy of choice in fulminating heart failure If ganglionic blockade appears adequate one of the longer acting agents can be substituted Mecamylamine is particularly good after the dose has been adjusted since the oral dose is the same as that which is effective parenterally

When ganglionic blocking agents given in combination with reserpine are inadequate parenteral veratrum should be given Continuous intravenous infusion is the most potent and effective but intramuscular injections are preferred when competent nursing care is unavailable since excessive hypotensive episodes are less likely to occur

After the blood pressure has been stabilized for 3 7 days and the general status of the patient seems adequate a permanent regimen should be instituted *A combination of rauwolfia and a ganglionic blocking agent is the therapy of choice* Oral rauwolfia should be substituted for parenteral reserpine A dose of 1 mg reserpine 250 mg whole root or 4 mg alseroxylon is usually given and after several months decreased to the smallest effective dose

As the effect of parenteral reserpine is lost one of the blocking agents is started and the dose gradually increased adjusted according to the standing blood pressure

When the blood urea nitrogen (BUN) is elevated it should be determined every 2 3 days while blood pressure is being regulated If the BUN should rise the pressure should be allowed to increase slightly by decreasing the dose of the blocking agent until the BUN again decreases to pretreatment levels As blood pressure is controlled for prolonged periods, progressive vascular deterioration is usually arrested and renal function improved unless damage was too severe before therapy was started

Drug Therapy in Hypertension is reviewed by Irvine H Page[5] (Cleveland Clinic) Blood pressure should not be lowered if it has been caused by cerebral arteriosclerosis This type can be recognized if an intravenous injection of a hypotensive drug causes the patient to become disoriented woozy or befuddled

(5) Postgrad. Med. 21 344 353 Ap 11, 1957

a 15 year period A diagnosis of hypertension was made pre operatively in 344 (11%) and 337 were available for study Of the 337 39 had renal tumors 119 hypoplastic or atrophied kidneys and 179 various renal conditions such as hydronephrosis tuberculosis calcareous pyelonephritis renal cysts pyonephrosis subcapsular calcified hematomas and aneurysms of the renal artery

The diagnosis of hypertension was made after complete study and was recorded as mild in some but moderate and sometimes severe in most A good early effect was recorded if after surgery the blood pressure remained less than 140/90 during the hospital stay and a good late effect was noted if this level was maintained for more than a year

Of the 39 patients with tumors a good early effect was seen in 12 After a year however only 5 had normal blood pressure Of 100 with atrophic pyelonephritis 63% showed a good effect when discharged from the hospital and of 64 who were followed 1 year or more the blood pressure remained normal in 55% Of 169 with other unilateral renal diseases 38% showed a good early effect which continued 1 or more years in 25% This arbitrary division into good or poor effect refers chiefly to blood pressure Patients whose blood pressure showed no decrease claimed subjective improvement with disappearance of headaches and better general health

The early effects of removal of a diseased kidney are often striking and usually occur within 3 days of surgery In no case was benefit delayed several months if not apparent immediately after surgery

Histologic study of the removed kidneys revealed no specific differences between patients with hypertension and those without Vascular sclerosis infection and calculi were present in both groups

There is no method for accurately selecting patients who may benefit from nephrectomy However many patients having nephrectomy for severe unilateral renal disease do benefit Unless surgery is specifically contraindicated it is unwise to postpone nephrectomy for fear of not relieving the severe hypertension The operation carries little risk and usually the disease is so far advanced it is not expedient to save the kidney

age the minimum was reached at 2 hours and pressure returned to control levels in 4 12 hours

Average total daily dose was 29 mg (range 3 90 mg) divided into 3 doses/day Therapy was begun with 2 mg at 8 a m 2 p m and 10 p m increasing the dose by 2 mg every 48 hours until a hypotensive effect was obtained The individual doses during the day were then changed if necessary to obtain the least diurnal variation An additional dose can be given at 5 or 6 p m if the evening pressures are high or the morning dose can be reduced or omitted if pressures are low at this time

Of 8 patients with grade IV changes in optic fundi 2 reverted to grade III and 6 to grade II Of 15 patients with grade III fundi 13 reverted to grade II and 1 to grade I In 7 with grade II changes 6 reverted to grade I In 7 patients cardiac size measured by x ray decreased 1 3 cm and in 4 electrocardiographic evidence of left ventricular hypertrophy reverted to normal Albuminuria tended to lessen In 9 patients with elevated blood urea nitrogen before treatment levels decreased to normal in 5 and toward normal in 1 remained unchanged in 2 and increased in 1

The commonest side effect was constipation (88%) which could be controlled by neostigmine 15-45 mg orally before breakfast and/or laxatives Impaired visual accommodation and postural faintness occurred in 27% Impotence partial or complete, difficulty in emptying the urinary bladder and dry mouth were common In most patients development of tolerance was slight or nonexistent Three patients died while being treated or shortly thereafter 2 of malignant hypertension and uremia and the third of myocardial infarction Treatment was discontinued in 4 because of abdominal distention and vomiting obstipation and low grade paralytic ileus Side effects were typical of those experienced with other ganglion blocking agents Adding small doses of hydralazine caused slight additional hypotension in 3 of 13 patients Adding reserpine produced an additional hypotensive effect in 5 of 11 patients

Results of Nephrectomy in Hypertensive Patients Gershom J Thompson[7] (Mayo Clinic and Found) reviewed the results of unilateral nephrectomy in 3 000 patients over

(7) J L 1 77 358 363 M ch 1957

For 48 hours before any of these tests sedatives or narcotics are prohibited Potassium thiocyanate barbiturates Demerol® morphine chloral hydrate and codeine and antihypertensive drugs can interfere with the tests

The pharmacologic tests are not always successful or accurate If doubt remains measurement of the quantity of epinephrine and norepinephrine in the urine and the blood may be helpful The pheochromocytoma must be secreting epinephrine or norepinephrine spontaneously or be induced to secrete during the period that blood or urine is being collected

A pheochromocytoma may occur wherever chromaffin tissue is present predominantly along the great vessels in the abdomen or thorax If a tumor is not found in the adrenal glands these sites must be inspected If blood pressure does not fall and remain down after a tumor is removed another tumor should be suspected and searched for Wide variations in pressure may occur during operation After removal of the tumor pressure may fall alarmingly Levarterenol bitartrate should be given intravenously as long as necessary

During the past 11 years 8 873 pharmacologic tests have been carried out for pheochromocytoma at the Mayo Clinic without serious side reactions A correct preoperative diagnosis was made on 51 patients and 61 tumors were found No deaths or untoward effects occurred during tests before during or immediately after operation

Further Experience with Apresoline® in Toxemia and Hypertension of Pregnancy Humbert L Riva Woodrow L Pickhardt Robert E Holzworth and Robert L Sherman[9] (Walter Reed Army Hosp) treated 67 pregnant patients of whom 34 had pre eclampsia 19 hypertension of labor 8 hypertensive vascular disease 3 hypertension with superimposed toxemia 2 eclampsia and 1 pre eclampsia with chronic glomerulonephritis The drug was given intravenously to 52 patients orally and intravenously to 9 and orally or subcutaneously to 6 For intravenous injection 20-40 mg Apresoline® was given slowly over 5 10 minutes The blood pressure was recorded at 10 20 second intervals during injection and only enough drug was given to reduce the pressure to normal

Maximal blood pressure response usually occurred 45 60

(9) Am J Obst & Gynec 72 48 55 J ly 1956

Pheochromocytoma a tumor of chromaffin tissue that secretes pressor amines is not common but is diagnosed more readily now A correct diagnosis is lifesaving The subject is reviewed by Walter F Kvale Grace M Roth William M Manger and James T Priestley[8] (Mayo Clinic and Found)

Pheochromocytomas secrete epinephrine and norepinephrine in varying amounts If secretion is intermittent manifestations are episodes of sudden rapid rise in blood pressure with tachycardia great anxiety severe headache pallor particularly of the face numbness tingling and coldness of the hands and feet sometimes nausea and vomiting pain in the epigastrium and excessive sweating One or more of these may be lacking Attacks commonly last 10 15 minutes but may persist several hours Frequency varies from 20/day to once every 2 3 months Between attacks health is usually good Severe episodes may lead to death from cerebral hemorrhage shock or pulmonary edema

The patient with sustained hypertension due to pheochromocytoma may have more or less continuous secretion of pressor substance from the tumor Some may have attacks during which blood pressure rises even higher The clinical picture may be identical with essential hypertension Usually the syndrome is increasingly severe headaches excessive perspiration nervousness and tremulousness The patient is almost always thin BMR is invariably above plus 10% and elevated blood glucose is common

Pharmacologic tests are of two types Histamine tetraethylammonium bromide and methacholine chloride stimulate discharge of pressor substances from the tumor and are useful between episodes They produce attacks similar to those which occur spontaneously If the resting blood pressure is less than 170 mm Hg systolic and 110 mm diastolic 0 05 mg of histamine base in 0 5 ml normal saline is injected intravenously The test is considered positive for pheochromocytoma if after initial decrease blood pressure rises at the end of 2 minutes far above the level reached in a cold pressor test

The Regitine® test is given to patients with sustained hypertension The agent is injected rapidly in a dose of 5 mg intravenously The test is positive if systolic blood pressure decreases more than 35 mm and diastolic more than 25 mm

(8) Circulation 14 622 630 October 1956

and decreased glomerular filtration rate However in none was the right ventricular end diastolic pressure elevated above 14 mm Hg and this finding most consistently differentiated the cardiac group with no evidence of salt and water retention from that group with such retention Neither at rest nor during exercise were cardiac output pulmonary artery pressure systemic arterial pressure renal plasma flow and glomerular filtration rate consistently or significantly different in the two groups

Findings do not support the forward failure concept as the main cause of edema in congestive heart failure They are more consistent with the backward failure concept in suggesting that critical elevation of right ventricular end diastolic pressure and peripheral venous pressure is the more important determining factor However reductions in cardiac output and glomerular filtration rate may also increase renal retention of sodium and water

► [For more than a decade there has been a difference of opinion concerning the relative importance of left sided failure versus right sided failure and diminished glomerular infiltration versus increased tubular reabsorption of sodium in regard to the pathogenesis of cardiac edema. This study and the two following ones as well as many others which have appeared in the recent literature all seem to agree in indicating that while diminished glomerular infiltration is the usual finding in patients with congestive failure it has little or nothing to do with sodium retention and edema formation These studies likewise indicate that increased residual blood in the right ventricle with rise in end diastolic pressure (back pressure) is more important than diminished cardiac output in causing the kidney to retain sodium The exact mechanism whereby this is brought about is still obscure It appears that alterations in the distribution of extracellular fluid, and possibly of blood activate the adrenals through some unknown mechanism and cause increased formation of aldosterone with subsequent retention of sodium by the renal tubule. Water retention appears to be secondary to that of sodium under most circumstances but there is also evidence that water retention may occur independently of sodium accumulation in some patients —Ed]

Relation of Negative Intraventricular Pressure to Ventricular Volume The nearly empty rhythmically beating ventricle can suck fluid into its cavity Negative intraventricular pressures have been recorded throughout diastole indicating that a sucking force exists even when the myocardium is relaxed Gerhard A Brecher and Abbott T Kissen (Ohio State Univ) repeated these experiments under static conditions in the quiescent but viable ventricle in anesthetized open chest dogs

Under static conditions the negative intraventricular

(2) C lat on R 5 157 162 M rch 1957

minutes after injection of the drug and the effect lasted 1-6 hours Dosage varied from 20 to 40 mg but the optimal *dose was 40 mg intravenously Some patients received mul* tiple doses The dosage subcutaneously varied up to 160 mg and orally up to 400 mg daily The results were variable although 3 patients showed good responses Occasionally this type of therapy may be useful in a patient not in labor

Characteristic signs of a good response were facial flush tachycardia and a bounding pulse noted in all patients who received the drug intravenously Pulsating or throbbing headaches were rare and required no therapy No other un*toward symptoms were noted In the 67 cases there* were 5 stillborn infants and 2 neonatal deaths of premature or immature infants Infant mortality of 7% was not attributed to the use of Apresoline® Some mothers of stillborn infants had placental infarction and premature separation of the placenta Fetal heart tones were unaffected by the drug

Apresoline® is highly recommended for control of the hypertensive aspects of pre eclampsia and hypertension of pregnancy

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PATHOLOGIC PHYSIOLOGY

Relationship of Cardiovascular and Renal Hemodynamic Function to Sodium Excretion in Patients with Severe Heart Disease but without Edema was investigated by William Hollander and Walter E Judson[1] (Boston Univ) Patients in congestive heart failure with peripheral edema have impaired sodium excretion which may persist after recovery from clinical heart failure In patients with heart disease but without edema no obvious disturbance in renal excretion of sodium was found

Patients with signs and symptoms of pulmonary congestion but with little or no evidence of right sided heart failure did not necessarily develop salt and fluid retention when on a moderately high sodium intake and most had no obvious defect in excretion of sodium when loaded heavily with hypertonic saline These patients had pulmonary *hypertension* reduced cardiac output decreased renal plasma flow

(1) J Clin I t 35 970 979 Sept mber 1956

nificant effect on renal plasma flow and glomerular filtration rate Mean arterial blood pressure was also unaltered With venous pressures higher than this the renal plasma flow and glomerular filtration rate decreased significantly The constant renal plasma flow and glomerular filtration with the smaller increases in pressure could be ascribed to a decreased pressure gradient from renal artery to vein due to a fall in resistance within the renal circuit at the capillary level just compensating for the retarding influence of the venous pressure As the venous pressure increased the mechanical effect hampered the capillary outflow Filtration fraction was not significantly altered even at high levels of renal venous pressure because of proportionate changes in glomerular filtration rate and renal plasma flow

Elevation of renal venous pressure up to 120 mm of saline had no significant effect on sodium and water excretion but at higher levels further increments in pressure produced progressive reduction in excretion Above 295 mm of saline where glomerular filtration rate also decreased the decrease in sodium and water excretion was more marked More sodium and water was absorbed by the tubules because the retarded flow of urine through them allowed more time for the normal absorption mechanisms to operate When pressure in the renal vein was released the sodium and water excretion tended to recover although incompletely in some

Potassium clearance was not significantly reduced until venous pressure was raised to 320 mm of saline when glomerular filtration rate also fell The values of potassium clearance tended to support the hypothesis of tubular secretion of potassium Urea clearance was also not significantly reduced until the glomerular filtration rate was diminished indicating that the load reabsorptive relation for urea was unaffected up to pressures of 295 mm of saline When this load reabsorptive relation was disturbed by decrease in glomerular filtration rate the urea clearance was significantly reduced

These conclusions cannot be directly applied in explaining the pathogenesis of fluid and electrolyte retention in clinical congestive heart failure Elevated venous pressure is only one factor in congestive heart failure which causes

transmural pressure is caused by elastic forces of the ventricular wall and the degree of negativity is inversely related to the ventricular volume Any increase in the elastic force which might follow weak myocardial contractions does not appear to alter significantly the general level of the negative intraventricular transmural pressures A complete ventricular pressure volume curve is S shaped with a negative limb for small volumes and the familiar positive limb for large volumes The suction force of the left ventricle is greater than that of the right The wall tension changes least in the range of 0 and slightly positive pressures The modulus of elasticity of the walls increases with extreme degrees of emptying and filling

These experiments show that under static condition elastic forces of the ventricular walls tend to expand the cavities and produce negative intraventricular transmural pressures and that the effect is greater the smaller the ventricular volume These observations may be applicable to the beating heart and may indicate that a ventricle with a small residual volume would create a negative transmural pressure hence suction toward the end of diastole This would explain the previously observed negative intraventricular pressures and ventricular filling by suction which lasted throughout diastole Elastic forces responsible for ventricular filling by diastolic suction under relatively static conditions can occur only when residual volume of the ventricle is below a certain amount Knowledge of this volume would aid in predicting the possible contribution of diastolic suction to ventricular filling under various conditions

Experimental Study on Effect of Increased Renal Venous Pressure on Renal Function with Special Reference to Mechanism of Fluid Retention in Congestive Heart Failure K N Gour and H M Chaudhuri[3] (Med College Agra) performed acute experiments in dogs elevating the renal venous pressure by graded increases and studied the effects on kidney function by clearance technics Renal function was measured separately and simultaneously in the two kidneys but pressure was raised only in the left

Acute elevations of renal venous pressure from a mean average normal of 70 mm of saline up to 295 mm had no sig

(3) I d Heart J 8 163 193 May 1956

heart failure The reduced filtered sodium which results from the lowered glomerular filtration rate apparently is not the important factor responsible for sodium retention

Effect of Prednisone in Treatment of Refractory Cardiac Edema Prednisone and prednisolone have been shown to be at least three times more potent therapeutically than cortisone and hydrocortisone and to have a diminished effect on electrolytes Prednisone induced diuresis has been reported in a series of patients with cardiac edema refractory to treatment Allen D Riemer[5] (Univ of Colorado) reports a case of refractory anasarca in a patient with severe coronary artery disease treated with prednisone who subsequently regained response to mercurial diuretics The mechanism of action is unknown but it is postulated that prednisone might act by decreasing the output of aldosterone through its action in depressing the output of all adrenal cortical steroids

The present observations warrant extensive investigation regarding the possible value of prednisone in the management of some cases of refractory cardiac edema

Man 47 had a myocardial infarction at the age of 34 and 3 recurrences thereafter Congestive failure had become progressively more resistant to frequent and large doses of mercuhydrin even when administered intravenously Low salt diet, Diamox ® increased digitalis and repeated mercurial injections were ineffectual and he showed extreme generalized failure dyspnea in the sitting position cyanosis marked engorgement of neck veins further enlargement of the heart to right and left muffled heart sound with gallop rhythm coarse rales pulsating liver palpable spleen distended abdomen with shifting dulness and fluid wave sacral edema and elephantiasis like legs He was considered in terminal state

Prednisone 2 5 mg 3 times daily was started There was immediate increase of urine output which became especially pronounced after injections of previously ineffective mercuhydrin the volume going as high as 8 600 cc in 24 hours The signs and symptoms of myocardial failure steadily diminished and eventually disappeared By the 32d day of treatment he no longer had rales dyspnea cyanosis hepatosplenomegaly ascites peripheral edema hypotension muffled tones murmurs or gallop rhythm By the 60th day he returned to full time light work For the 9 months he has continued taking prednisone he has remained compensated taking Diamox® only twice weekly as a diuretic maintenance digitalis quinidine and low salt diet

(5) B ll J h H pk H p 98 445-453 June 1956.

edema yet in itself it can cause significant changes in electrolyte metabolism which may contribute to the genesis or maintenance of edema

Influence of Posture on Renal Function in Heart Failure. Studies have shown a low glomerular filtration rate low renal blood flow with a high fraction of renal plasma flow filtered and retention of sodium in patients with heart failure as compared with normal subjects A E Doyle and J M Merrill[4] (Post Grad Med School London) studied 18 patients with congestive heart failure due to rheumatic or congenital heart disease to determine whether the diminished glomerular filtration rate is responsible for diminished sodium excretion

Studies were made at the same time of day to avoid diurnal variations in renal function Loading and maintenance doses of inulin and para aminohippuric acid were given intravenously After control collections the patients were tilted to a 60 degree feet down position and test collections made

Although the initial sodium excretion in all patients was low there was a further fall when they were tilted of the same order of magnitude as the fall in urinary volume Despite this concentration of sodium in the urine rose Potassium excretion was slightly raised compared to normal and tilting produced a fall in potassium excretion and rise in urinary potassium concentration but not as marked as the changes in sodium

Changes in urine volume apparently were due in part to corresponding changes in filtration rate and in part to changes in reabsorption During tilting when the fall in the filtration rate occurred there was a marked reduction in urine volume with no accompanying rise in the urine plasma inulin ratio Percentage changes in urine volume were closely related to percentage changes in inulin and para aminohippuric acid clearance but were not constantly associated with changes in filtration fraction In general a rise in urine volume tended to be associated with a rise rather than a fall in filtration fraction but the correlation was not close

These findings confirm the low glomerular filtration rate and renal plasma flow and the high filtration fraction in

(4) Clin Sc 16 15 162 February 1957

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(5) B ll J h H pk H p 98 445-453 J 1956

Treatment of Low Salt Syndrome in Congestive Heart Failure by Controlled Use of Mercurial Diuretics In cardiac patients with fluid retention two types of electrolyte imbalance have been associated with transient refractoriness to mercurial diuretics hypochloremic alkalosis and hyponatremia with hypochloremia The latter is characterized by drowsiness weakness lethargy loss of appetite nausea and vomiting and occasionally abdominal or muscular cramps These are accompanied by successive depression of urine volume decreased excretion of chloride unresponsive to mercurial diuretics progressive weight gain and rising non protein nitrogen content of the blood

Most patients with refractory edema due to heart failure have normal plasma electrolyte concentrations These patients are unable to handle water as well as salt Salt intake may be rigidly restricted fluid intake is not The result is fluid retention further expansion of extracellular fluid volume and consequent electrolyte dilution Overhydration with expansion of *fluid volume and dilution of electrolyte* is the most important etiologic factor in this syndrome which should be termed the dilution syndrome rather than the low salt syndrome

According to Albert L Rubin and Warren S Braveman[6] (Cornell Univ) therapy should aim to mobilize the excess fluid in the expanded extracellular fluid space rather than to elevate extracellular fluid sodium content Hypertonic saline does not improve clinical status it often results in further weight gain and progression of already distressing symptoms

Responsiveness to mercurial diuretics is restored by using Diamox[®] and ammonium chloride to produce rise in plasma chloride concentration necessary to provide an adequate chloride load to the renal tubules This is achieved when urinary chloride concentration has risen to over 40 mEq/L Once the necessary hyperchloremia has been attained mercurials induce a diuresis and each liter of urine excreted has a sodium content lower than extracellular fluid As a result with fluid intake restricted sodium concentration of the extracellular fluid rises toward normal

Production of acidosis in a patient who already has azo

(6) Circulation 13 655-663 May 1956

temia is potentially hazardous and continued close clinical and laboratory observations are essential The indication that the necessary acidosis has been reached is a rise in urinary chloride concentration This is unrelated to a specific level of plasma pH or plasma chloride concentration

Body Composition Total Body Water and Electrolytes Intravascular and Extravascular Phase Volumes The methods interpretation and most important findings are reviewed by Francis D Moore James D McMurrey H Victor Parker and I Caryl Magnus[7] (Harvard Med School)

Plasma volume can be measured by Evans blue dye red cell volume by radiochromate tagging of red cells blood volume by the sum of the dye plus radiochromate extracellular fluid volume by radiobromide dilution which measures an area of body water similar to that occupied by chloride total body water by deuterium dilution total exchangeable potassium by equilibration of radiopotassium 24 hours after injection total exchangeable sodium by radiosodium and total exchangeable chloride by radiobromide dilution (radiobromide is used because the half life of radioactive chloride is only 37 3 minutes)

A multiple simultaneous technic has been evolved which allows measurement of several of these constituents in 36 hours Blood volume and total body water are measured on the first morning then radiobromide is injected and after a 16 hour incubation is sampled next morning Radioactive sodium and potassium are then injected and the final sample is taken for sodium and potassium equilibrium on the third morning

Using this technic normal values for a man aged 60 weighing 70 kg were found to be large vessel hematocrit 44% plasma volume 3 150 ml 4 5% body weight red blood cell volume 2 100 ml 3% body weight blood volume 5 250 ml 7 5% body weight whole body hematocrit 40% total body water 39 8 L 56 8% body weight extracellular water 16 4 L 23 4% body weight total exchangeable chloride 2 030 mEq or 29 mEq/kg plasma chloride concentration 105 mEq/L carbon dioxide combining power 27 mEq/L total exchangeable sodium 2 870 mEq plasma sodium concentration 140 mEq/L serum osmolarity 285

(7) Metabolism 5 447-467 July 1956

mOsm/L total exchangeable potassium 3 300 mEq or 47 mEq/kg and plasma potassium concentration 4 mEq/L In the normal woman absolute values are less than in the male but relative values are approximately the same

In the syndrome of depletion due to chronic infection chronic starvation malignancy repeated trauma or prolonged illness some cachexia is usually visible and patients appear depleted In terms of their actual observed weight they have a normal total blood volume with high plasma and low red cell volume Total body water is normal with an increased extracellular portion Total sodium and chloride are very high and the Na K ratio is reversed Intracellular water and total exchangeable potassium are low and residual sodium is high The extracellular parameters remain normal for the patient s normal body weight while the cellular mass and intracellular constituents shrink markedly

Patients with chronic disease who have a low serum sodium concentration and slightly elevated serum potassium may be assumed to have a whole body hypotonicity Their low hematocrit value is due to high plasma and low red cell volume The depression of serum sodium is not dehydration and is not related to sodium loss when extrarenal losses are absent but represents relative overhydration Such patients are vulnerable to indiscriminate blood transfusions and intravenous infusions It is important to improve diuresis of water and sodium and to replenish energy

In patients with advanced congestive failure due to mitral stenosis the composition differs from starvation depletion in that total body water and exchangeable sodium are absolutely increased Blood volume body water extracellular volume and total exchangeable chloride and sodium are high serum concentration of sodium and chloride and serum osmolarity are slightly low and the Na K ratio is the highest observed in any disease Intracellular water is near normal total and intracellular potassium are low and residual sodium is high

Unloading of salt and water are therapeutically important Indiscriminate use of ammonium chloride and mercurial diuretics is hazardous since a chronic metabolic aci

dosis may result in further accumulation of extracellular salt water Osmotic diuretics may be useful Most important in mitral stenosis is adequate surgery Restoration is quickly begun after surgery but it may take a year before body com position is fully returned to normal

Water Intoxication and Serum Hypotonicity are due to re tention of a large amount of water in osmotic excess of elec trolytes Serum hypotonicity is common to three syndromes which differ in pathogenesis prognosis and treatment Vic tor Wynn[8] (St Mary s Hosp Med School London) recom mends the use of terms primary water retention to de scribe body fluid dilution due mainly to retention of water in excess of electrolytes sodium depletion syndrome when hypotonicity is due mainly to loss of sodium salts and asymptomatic hyponatremia or symptomless hypotonic ity when serum sodium is low but no symptoms are present

Serum sodium levels of 125 133 mM /L or lower with corresponding reduced chloride levels are common in pa tients with chronic wasting diseases and after prolonged par enteral fluid therapy The hypotonicity is persistent and un affected except temporarily by treatment with salt thus dis tinguishing it from true sodium depletion and is not cor rected by water restriction thus distinguishing it from ex cessive water retention The cause is unknown It is usually associated with a poor prognosis The patient has no symp toms referable to hypotonicity shows progressive weight loss and appears wasted and the skin shows loss of elastic ity Plasma proteins are usually low with a reversed albumin globulin ratio Urine volume is normal with a low specific gravity and its sodium content is not abnormal No treat ment is indicated for asymptomatic hypotonicity

In the syndrome of sodium depletion without water deple tion the history reveals a large negative sodium balance with free intake of water Symptoms are usually gradual in onset with apathy and weakness sometimes restlessness and anx iety postural faintness anorexia nausea vomiting and muscle cramps There may be weight loss and the appear ance is haggard Tissue turgor and elasticity are lost Blood pressure especially pulse pressure is low and the pulse rate is rapid Central venous pressure is reduced veins are col

(8) M t bol m 5 490-499 J ly 1956

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cellular fluid volume and restores renal function with a return of osmotic regulation In water intoxication extracellular fluid volume is already increased Isotonic infusions will increase it further without appreciably raising serum sodium and without dehydrating the cells Renal function is not improved and cardiac failure and pulmonary edema may be produced

Hydrothorax in Congestive Heart Failure The etiology of pleural effusion and the factors determining the side of occurrence in congestive heart failure has been of interest for years It was noted early that unilateral pleural effusions associated with congestive heart failure affected predominantly the right side Various explanations have been offered George A Race Charles H Scheifley and Jesse E Edwards[9] (Mayo Clinic and Found) reviewed autopsy data on 290 patients with hydrothorax due to congestive heart failure

Of those with unilateral effusions 24 had it in the right pleural space and 11 in the left—a ratio of slightly more than 2 1 Of the total patients 279 had fluid in the right pleural space and 266 in the left *The traditional predominance of* right over left was confirmed but the difference is less striking than was formerly emphasized

Previous investigations have refuted the hypothesis of compression of the azygos vein and experiments have shown the pleural effusion to be a dynamic process with complete turnover of pleural fluid in an hour thus eliminating *lymphatic obstruction alone as the factor Pulmonary* edema was present grossly and microscopically in 177 of the 290 patients (61%) with hydrothorax due to congestive failure This high percentage is significant and suggests that pulmonary edema might be a factor although its absence in 39% of the patients means it cannot be the only factor No consistent correlation was found between the presence of pleural effusion and various inflammatory processes In 24 of the 60 patients with associated pulmonary infarctions hydrothorax was contralateral to the unilateral pulmonary infarct In 36 effusion and infarction were correlated

Left hydrothorax did not predominate over right in any one type of heart disease No one factor could be assigned as the cause of pleural effusion in congestive heart failure In

(9) Am J M d. 22 83 89 Janu ry 1957

lapsed and the limbs are pallid and cold Usually there are muscle weakness and sweating Hematocrit and plasma proteins and often serum potassium are increased Nonprotein nitrogen is usually elevated and may be very high Urine volume is low specific gravity is elevated and proteins casts and ketone bodies are usually present Urinary sodium content is zero or very low except in Addison s disease and renal diseases Treatment consists of correction of hemoconcentration Normal saline is effective Hormones may be required in adrenal insufficiency

In the syndrome of water intoxication, the history reveals a large positive water balance acutely or gradually produced In acute cases there is a sudden onset of mental disturbances disorientation weakness fits or coma In chronic cases onset is usually gradual and symptoms are extreme prostration weakness sleepiness disorientation apathy, anorexia and fits There is usually a weight gain the appearance is normal and the skin shows no abnormality Blood pressure is normal or raised and pulse rate is normal Central venous pressure is normal veins are full and the limbs are normal in color and warm The nervous system signs are muscle weakness diminished or absent tendon reflexes no sweating and in acute cases coma and extensor plantar responses There may be overbreathing in acute cases Hematocrit and plasma proteins are low serum potassium may be normal or low nonprotein nitrogen is normal unless previously raised and serum bicarbonate is low in acute cases Urine volume may be low or high specific gravity is usually low and sodium content is often high Hypotonicity must be corrected by hypertonic saline and water restriction Normal saline is ineffective and dangerous

In water intoxication symptoms may be due to overhydration of cells To correct this restricted water intake is essential In mild cases urine excretion and insensible water loss will soon correct the abnormal hypotonicity In urgent cases hypertonic saline is effective Diagnosis must be certain and treatment used cautiously in patients with cardiac failure The amount given should raise serum sodium by about 10 mM /L and not more unless there are definite indications Isotonic saline is effective in treating sodium depletion because it rapidly corrects reduced plasma and extra

cellular fluid volume and restores renal function with a return of osmotic regulation In water intoxication extracellular fluid volume is already increased Isotonic infusions will increase it further without appreciably raising serum sodium and without dehydrating the cells Renal function is not improved and cardiac failure and pulmonary edema may be produced

Hydrothorax in Congestive Heart Failure The etiology of pleural effusion and the factors determining the side of occurrence in congestive heart failure has been of interest for years It was noted early that unilateral pleural effusions associated with congestive heart failure affected predominantly the right side Various explanations have been offered George A Race Charles H Scheifley and Jesse E Edwards[9] (Mayo Clinic and Found) reviewed autopsy data on 290 patients with hydrothorax due to congestive heart failure

Of those with unilateral effusions 24 had it in the right pleural space and 11 in the left—a ratio of slightly more than 2 1 Of the total patients 279 had fluid in the right pleural space and 266 in the left The traditional predominance of right over left was confirmed but the difference is less striking than was formerly emphasized

Previous investigations have refuted the hypothesis of compression of the azygos vein and experiments have shown the pleural effusion to be a dynamic process with complete turnover of pleural fluid in an hour thus eliminating lymphatic obstruction alone as the factor Pulmonary edema was present grossly and microscopically in 177 of the 290 patients (61%) with hydrothorax due to congestive failure This high percentage is significant and suggests that pulmonary edema might be a factor although its absence in 39% of the patients means it cannot be the only factor No consistent correlation was found between the presence of pleural effusion and various inflammatory processes In 24 of the 60 patients with associated pulmonary infarctions hydrothorax was contralateral to the unilateral pulmonary infarct In 36 effusion and infarction were correlated

Left hydrothorax did not predominate over right in any one type of heart disease No one factor could be assigned as the cause of pleural effusion in congestive heart failure In

(9) Am J M d. 22 83 89 J ary 1957

every category except mitral heart disease combined left and right failure predominated over right alone Auricular fibrillation was more commonly associated with unilateral left sided than with unilateral right sided hydrothorax

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ELECTROCARDIOGRAPHY AND ARRHYTHMIAS

Clinical Implications of Errors in Electrocardiographic Interpretation Heart Disease of Electrocardiographic Origin Undue reliance on the ECG diagnosis and management of heart disease has created many problems Myron Prinzmetal Alfred Goldman Rashid A Massumi Louis Rakita Lois Schwartz Rexford Kennamer Kiyoshi Kuramoto and Hubert Pipberger[1] emphasize the consequences of erroneous or overzealous diagnosis of heart disease based on ECG alterations that are not necessarily diagnostic of such disease

In the absence of heart disease the most important single factor in the development of subjective cardiac symptoms is the erroneous interpretation of some benign ECG changes discovered on routine examination Other factors are the increasing availability of the ECG, increased number of lay publications on heart disease high incidence of chest pain often unrelated to heart disease and lack of adequate interchange of information between the clinician and the ECG interpreter The incidence of heart disease of electrocardiographic origin is increasing An average physician caring for cardiac patients sees 10 25 such cases a year

Symptoms vary among patients and depend on circumstances that precede their onset such as illness or death due to heart disease in members of the family or friends and articles in the lay press concerning heart disease Anxiety and chest pain are common weak spells fainting tendencies and palpitation are often reported Discovery of some minor changes in the ECG leads to marked anxiety and heart consciousness that often causes true iatrogenic disease usually preventable by the proper approach

(1) J A M A 161 138 143 May 12 1956

Tenderness on firm finger tip pressure over the anterior chest wall is the most significant finding on physical exam ination A correct diagnosis depends on the physician s high index of suspicion and awareness of two facts (1) Chest pain does not always represent heart disease it occurs as often in patients with normal hearts as in those with coro nary disease (2) S T segments and T wave changes do not invariably denote myocardial abnormality and may some times be caused by the patient s fear

Treatment is prophylactic and therapeutic The phrase these changes may also occur in patients with normal hearts should be added to the interpretation of tracings with equivocal S T segment and T wave changes Curative therapy consists chiefly of reassurance

Deep myocardial damage does not produce much change in the ECG but relatively insignificant lesions of superficial layers may cause marked alterations The ECG is a useful diagnostic aid but its interpretation is often uncertain The most reliable guide in diagnosis and management of the pa tient with cardiac symptoms is the patient s clinical state

► [This communication and the two following it emphasize the frequency of erroneous diagnosis and unnecessary restriction of life as the result of excessive reliance on the electrocardiogram Perhaps the two commonest errors are the assignment of importance to insignificant and physiologic variations of the T wave and the assumption that minor depression of the S T segment and particularly the junction following exercise is a cer tain indication of coronary d sease Such errors would be avoided if phy sicians placed more emphasis on the clinical evaluation of patients and particularly of the r histories and of their clinical response to exercise and less emphas s on minor electrocardiographic changes —Ed]

Effects of Nonpathologic Factors on Electrocardiogram I Results of Observations under Controlled Conditions

Irving L Rosen and Manuel Gardberg (Louisiana State Univ) studied the effects on ECG s of exercise taking food smoking change in posture and changes in respiratory level

In the normal subject exercise increases the heart rate and decreases the P R and Q T intervals The height of the P wave may increase and the auricular T wave become more prominent Since the auricular T wave may continue beyond the QRS complex this may depress the first portion of the RS T segment After exercise many persons presumably because of a change in respiratory midposition show QRS changes indicating a change in the ECG position of the

(2) Am H rt J 53 494 504 Ap 1 19 7

heart All the normal subjects demonstrated RS T segment and/or T wave changes immediately after exercise which rapidly cleared The T axis swings to the right to the left or remains unchanged and generally diminishes in amplitude In lead III, inversion of the T wave would still be considered normal but the flat to inverted T_1 and inverted T_2 and T_3 would be considered abnormal by most electrocardiographers

When the rate increases the T waves and RS T segment of any lead tend to change in a direction opposite to that of the main deflection of the QRS complex in that lead The RS T segment shifts occurred commonly after exercise and contrary to published reports it was not rare to shift 1 mm or more These RS T shifts tended to be proportional to and opposite in direction from the main deflection of the QRS in that lead and were proportional to the rate

Heart rate increases in most persons after a meal Marked changes are seen in RS T segments and T waves reaching a maximum in about 1 hour and lasting 2 3½ hours similar to those resulting from exercise but not as marked T wave changes following smoking are similar to those after exercise Smoking generally produces marked increase in rate which may be largely responsible for the changes noted Similar changes are induced by changing from the supine to the sitting position and may be exaggerated by deep breathing These changes are presumably secondary to those in the ECG heart position

Many persons have had the erroneous diagnosis of cardiac disease because of marked T wave changes which were not pathologic The criteria used heretofore are most inadequate especially applied to records not made under basal conditions The ECG must frequently be made under other than basal conditions but interpretation should consider the possible effects of nonpathologic factors The criteria selected by previous investigators in the evaluation of the exercise ECG must be revised

Influence of Meals on Long P R Intervals in ECGs of Young Men A P R interval in the ECG longer than 024 second is usually regarded as pathologic It is assumed that in a young person a long P R interval is caused by excessive vagal function and that it will become normal after

an injection of atropine sulfate and usually also after exertion

In examination of aviation candidates at the National Aviation Medical Center routine ECG s are made on a large group of young men aged 17 20 In ordinary medical practice ECG s are seldom made in this age group so little is known of possible deviations in young persons In the past 2 years C D DeLangen and G J Puister[3] observed in certain persons a P R interval far longer than the supposed normal 0 24 second Intervals as high as 0 38 and 0 4 second were observed in 8 young men 3 (2 previously reported) showed so called Wenckebach periods which disappeared after exertion The long P R intervals present in the morning surprisingly disappeared shortly after the midday meal In 1 Wenckebach periods which disappeared after a meal were observed again 1½ years later

Although in the literature it is assumed that eating exerts no influence on P R time this observation led to further investigation Among 6 others with a P R interval longer than 0 24 second the interval immediately became normal after physical exertion (20 knee bends) and after a meal Influence of a meal on the P R interval was additionally studied in 100 applicants aged 18 21 In 54 the interval before and after eating was the same After eating it was 0 01 shorter in 17 0 02 shorter in 18 0 03 shorter in 6 0 01 longer in 2 and 0 02 longer in 2 In 1 the P R interval was exceptionally long in the fasting state but reverted to normal after a meal

Atrial Electrocardiogram or P wave is the algebraic sum of the potential changes resulting from activation and repolarization of the atria Activation is primarily responsible for the P wave whereas restitution produces the T of the P wave (Ta) B van Lingen and J H Gear[4] present criteria for left and right atrial enlargement

Activation of the atria commences in the sinoauricular node in the right atrium and proceeds by contiguity of muscle tissue Therefore right atrial activity must precede in part activation of the left atrium The intrinsic deflection over the right atrium recorded by esophageal leads occurs during the first half of the P wave as recorded from the body

(3) N d l t jdsch genee k 100 1296-1299 M y 5 1956
(4) South Af ca J Lab. & Clin M d. 2 125 133 J 1956

surface whereas that from the left atrium occurs during the latter half By operation or catheterization these findings have been confirmed by evidence of an intrinsic deflection recorded from the right atrium before the left

The P waves of 12 lead ECG s were measured in 100 normal subjects 97 patients with mitral valve disease 55 with systemic hypertension 30 with chronic cor pulmonale and 93 with a variety of congenital heart anomalies The upper limits for the size of the P wave two standard deviations above the mean normal are 1 2 1 8 1 5 1 2 1 2 and 1 3 mm for the limb leads I II III aVR aVL and aVF respectively and 1 1 mm for precordial leads V_1 to V_6 The P wave was commonly biphasic in lead V_1 and the sum of both components was 1 1 mm or less in normal subjects Duration never exceeded 0 11 second

Left atrial enlargement is characterized by prolongation and notching of the P wave Lead V_1 commonly showed rounded negative component in the precordial leads Further to the left on the precordium the second portion of the notched P wave became abnormally large With this pattern having an amplitude above normal diagnosis of left atrial enlargement can be made though the P wave is not prolonged

Right atrial enlargement is characterized by a P wave which is pointed and does not exceed the upper limits of normal duration If notching is present in the precordial leads the second portion is small Lead V_1 may show a pointed positive P wave but more commonly shows a diphasic P wave with both components sharp Leads further to the left show peaked P waves and if notched the early peak is largest

Combined atrial enlargement may show a combination of both features Diphasic P waves in normal subjects are common only in lead V_1 When they occur further to the left they are commonly associated with congestive cardiac failure

Studies on Nature of Repolarization Process XIX Studies on Mechanism of Ventricular Activity Hubert Pipberger Lois Schwartz Rashid A Massumi and Myron Prinzmetal[3] (Los Angeles) studied electric recovery in the

( ) Am H rt J 53 100 174 J n 1957

hearts of 49 dogs placed in an incubator to approach a phys iologic situation Surface intramural and cavity leads were taken by unipolar plunge electrodes

Simultaneously recorded leads from the ventricular sur face and subendocardium showed positive T polarity on both sides of the wall in almost half on the left and almost three fourths on the right ventricle In 9 animals intracavitary leads simultaneous with subcutaneous leads from the region over the ventricle showed the leads from both cavities and from the chest wall to be positive confirming the results ob tained in the incubator Thus T wave polarity from opposite sides of the ventricular wall was not necessarily reciprocal This disagreed with previous reports probably because room temperature had cooled the myocardium or because of other unphysiologic changes in the earlier investigations

Timed leads from the ventricular surface and the under lying subendocardium showed that the subendocardium preceded the epicardium in repolarization by a statistically significant mean time difference suggesting that repolari zation occurs in most instances earlier in the subendocar dium than in the epicardium Electric recovery ended earlier in the right ventricle than in the left There was no signifi cant time difference between the T waves from the apex and base of each ventricle

The influence of thermal changes on repolarization was investigated by applying warm and cold saline to the epi cardial and endocardial surfaces Cold increased the nega tivity heat the positivity of the T wave When the area of thermal change was small local T wave changes occurred without changes in distant subendocardial or adjacent leads As the area increased reciprocal T polarity changes were seen in recorded leads from the other side of the ventricular wall and from the opposite side of the heart

Ischemic T wave changes were studied after ligation of coronary arteries In some instances T negativity was found on the surface close to the infarction Intramural explora tion of the infarcted area by plunge electrodes showed that T negativity was restricted to outer layers Warm saline ap plied to the surface usually reversed the T wave to positive indicating live tissue in these areas The same changes could be induced in the T waves secondary to premature ventricu

lar contractions and in left bundle branch block These results emphasize that the T wave is extremely susceptible to a wide variety of stimuli and may be altered by small changes in environment T wave changes must be carefully evaluated to avoid misinterpretation

Left Axis Deviation Electrocardiographic Pathologic Correlation Study Left axis deviation is one of the commonest ECG abnormalities Alone it is usually considered of little clinical significance and attributed to a leftward anatomic position of the heart to incomplete left bundle branch block or to left ventricular hypertrophy However none of these is a common cause and other factors some clinically important are more frequently responsible To evaluate this finding Robert P Grant[6] (Nat l Inst of Health) collected 672 consecutive cases in which complete autopsies were performed and ECG s had been recorded within 5 weeks of death Patients under age 30 years and those with QRS interval durations of 0 12 second or more were *excluded*

One third of all patients with left axis deviation showed myocardial infarction at autopsy Of 160 patients with proved infarction 67 had left axis deviation and 44 of these had the QRS deformity of anterolateral infarction Thus left axis deviation is more common in anterolateral infarction than in any other category of heart disease The mechanism of left axis deviation in this type of infarction is peri infarction block characterized by a diagnostically wide angle between the initial and the terminal QRS forces In 4 cases with proved infarction this angle was diagnostically wide but the characteristic Q waves were absent This pattern of infarction has not been previously recognized

Left axis deviation was seen in less than half the cases with proved left ventricular hypertrophy Neither severity of the hypertrophy anatomic position of the heart nor body build was significant in development of left axis deviation in these subjects Incomplete left bundle branch block is extremely rare as a cause of left axis deviation In left ventricular hypertrophy the left axis deviation represents a type of parietal block in the more distal parts of the left ventricular conduction network perhaps the result of myocardial fibrosis that accompanies marked left ventricular hypertrophy

(6) *Circulation 14 233 249 August 1956*

Marked left axis deviation was present in 17 subjects who showed no myocardial infarction or hypertrophy at autopsy but who were all relatively advanced in age and showed myocardial fibrosis and chronic coronary artery disease which may have produced a conduction defect similar to that seen in left ventricular hypertrophy Six patients with severe pulmonary disease had marked left axis deviation which may have resulted from reduced electric conductance of the emphysematous lung

In 15 cases left axis deviation and R deflections in pre cordial leads V_1 and V were present in the same tracing Over half of these were due to anterolateral peri infarction block and this is the most common cause of R deflections in the precordial leads associated with left axis deviation Other causes were severe pulmonary disease left ventricu lar hypertrophy and chronic coronary artery disease The left axis deviation in these cases is due to a parietal block in the left ventricle analogous to that seen in anterolateral peri infarction block

Mechanisms of QRS Complex Prolongation in Man—*Left ventricular conduction disturbances*—Robert P Grant and Harold T Dodge[7] (Nat l Inst of Health) collected 128 cases in which one or more tracings with normal ventricu lar conduction had been recorded before or after tracings with QRS prolongation This was the first controlled study of conduction defects of the QRS in man as the tracing with normal ventricular conduction served as the control

The QRS interval was prolonged 0 05 0 06 second over the control in most tracings In 23 it was prolonged by more than 0 08 second Division of left bundle branch block into complete and incomplete depending on whether or not the QRS duration exceeds 0 11 second does not ac count for the wide variation in QRS prolongation in com plete block cases Incomplete left bundle branch block (QRS interval prolongation to *only* 0 10-0 11 second due to a conduction defect in the left main bundle) must be rare as a stable form of QRS prolongation It has not yet been proved in man

In one third of the 128 cases the first 0 03-0 04 second of the QRS interval did not change in direction or magni tude with onset of QRS prolongation Therefore left bundle

(7) Am J M & 20 834 852 J 1956

branch block cannot have caused QRS prolongation in these cases Half the cases of this type had the QRS complex deformity of myocardial infarction in the control tracing and the QRS prolongation is related to peri infarction block Any tracing resembling left bundle branch block but with Q waves similar to those of infarction should raise the question of peri infarction block A Q wave in lead I exceeding 0 02 second occurred only in peri infarction block never in left bundle branch block and the same applied to V_6 In 14 cases the initial R wave in V_1 was 0 03 second or more None of the cases with left bundle branch block showed progressive diminution of the R wave from V_1 to V_4 but it was found in 3 cases of peri infarction block A basic characteristic of peri infarction block is the relative opposite directions of the initial terminal vector angles Most cases of left ventricular conduction disturbance with a Q wave in lead I prove to be due to peri infarction block with prolongation rather than to left bundle branch block with septal infarction as generally believed

Other cases with no change in initial QRS forces when prolongation developed showed varying degrees of left ventricular strain pattern in the control tracing Further hypertrophy accounted for the prolongation in certain of the cases and probably peri infarction prolongation accounted for the others The pattern of left ventricular strain is similar to anterolateral infarction with peri infarction block

Right ventricular conduction defects—Dodge and Grant[8] collected 80 cases in which tracings satisfied the criteria of right bundle branch block a QRS duration of 0 12 second or more with an S wave in lead I and a terminal R in V_1 In each case one or more tracings with normal QRS duration were obtained before or after that showing prolongation

In experimental right bundle branch block induced in animals the first part of the QRS complex is altered indicating a change in the way excitation enters the ventricles This does not occur in clinical right bundle branch block Excitation enters the ventricles normally The most likely explanation for this discrepancy is that the lesion lies more distal along the conduction pathways of the right ventricle than

(8) Am J Med 21 534 550 Oct ber 1956

it does in experimental right bundle branch block There is no period when right ventricular excitation is arrested or delayed in clinical right bundle branch block contrary to common beliefs but excitation instantly leaks out into the right ventricular myocardium when it reaches the site of the block

Deformity of the initial QRS forces due to myocardial infarction still may develop in the presence of right bundle branch block Thus Q wave criteria for diagnosis of infarction are valid except in strictly posterior infarction An initial R wave at V_1 of more than 0 04 second duration with a normal QRS interval duration is often diagnostic of strictly posterior myocardial infarction However this is not true in the presence of right bundle branch block because in this block the QRS complex at V_1 and V may be positive for the first 0 04 second

Coronary artery disease is the most common cause of acquired ventricular conduction defects and evidence of myocardial infarction was present in half of the cases 50% diaphragmatic and 50% equally divided among anterolateral anterior and posterior locations Infarcts with left ventricular conduction defects however were most often anterolateral whereas the diaphragmatic area was involved in only one third of the patients The right ventricular conduction network is supplied by the right coronary artery and its occlusion produces diaphragmatic infarction Another factor is peri infarction block often difficult to distinguish from bundle branch block in which the terminal QRS forces become opposite in direction to the initial forces The mechanism of peri infarction block is probably delayed spread of excitation to epicardium overlying a subendocardial infarction Consequently the last QRS forces are from the epicardial layers If the QRS interval is prolonged to 0 12 second or more the complexes resemble bundle branch block

Diagnostic Significance of Tall Upright T Waves in Chest Leads J Freundlich[9] (Vancouver B C) reports 110 cases (10 women and 100 men) in which very high T waves especially in the chest leads were the only abnormal sign in the ECG Ages ranged from 30 to 70 years

Frequent anginal attacks occurred in 17 patients (15 3%)

(9) Am H rt J 5 749 67 N mbe 1956

They had high T waves which later disappeared and were followed by characteristic signs of anterior infarction in 7 posterior infarction in 3 combined anterior and posterior infarction in 1 and subendocardial lesions in 6 In 2 patients the high T waves disappeared within 24 hours but in 15 they persisted for months or years before they were replaced by negative T or marked depression of RS T

A history of coronary occlusion 2 10 years previously was obtained from 33 patients (30%) High T waves persisted unchanged for 4 7 years of observation associated with signs of posterior infarction in 14 anterior infarction in 14 and no other abnormalities in 5 Six patients had severe aortic stenosis due to an old rheumatic endocarditis frequent precordial pain on exertion and persistent large T waves in the ECG

The largest group 54 patients who had high T waves in the precordial leads had frequent anginal attacks with no history of previous coronary occlusion and normal physical and laboratory findings In 5 patients the amplitude of the T waves decreased during a prolonged period of rest and during this time patients were free from angina

High T waves are associated with frequent anginal attacks on exertion The large number (50 7%) of patients with proved myocardial damage in follow up studies indicates that high T waves have pathologic significance The remaining 49% are still under observation and their T waves remain high

Wolff Parkinson White Syndrome a Frequent Disease in Childhood? This pre excitation syndrome has no definite clinical signs but displays a characteristic ECG pattern with a shortened P Q segment (0 055 0 1 second depending on age) a widened QRS complex (0 08 second varying with age) with a characteristic delta wave and frequent bundle branch block delayed intrinsic deflection in precordial leads derived from both ventricles and inverted S T segments and T waves

R H Tamm[1] (Univ of Zurich) reports on 17 children observed from 1948 through 1955 (10 during 1955) and 1 seen in 1938 13 were boys 5 were aged under 1 year and the oldest was 17 Among 5 500 children on whom ECG s

(1) H l et paed t acta 11 78 98 Ap 1 1956

were made incidence was 0 29% which is relatively high compared with other series and probably is due to the fact that about 500 had congenital heart defects

Paroxysmal tachycardia was registered in the ECG in 7 patients 3 had repeated clinical crises of tachycardia and 2 others had attacks of questionable severity All had supra ventricular occasionally ventricular tachycardia Since pre mature excitation and the Wolff Parkinson White syndrome are clinically silent the patient usually seeks medical help because of symptoms of paroxysmal tachycardia In older children and adults tachycardia is experienced as exceed ingly unpleasant heart sensations with racing heart beats precordial pain and cold hands and feet Other complaints are dizziness—even to unconsciousness—and not infre quently a special indescribable inner unrest Objectively the principal sign is ashen face with cyanotic lips

If paroxysmal tachycardia persists it may result in car diac edema hypostatic bronchitis and eventually oliguria etc Infants react to paroxysmal tachycardia by refusing food Vomiting (initial diagnosis was pyloric stenosis in one instance) is present with cyanotic attacks wheezing cough dyspnea or tachypnea The liver and heart are enlarged lung fields clear and diaphragm depressed In 1 patient x ray suggested pneumonia Body temperature is generally in creased and white blood cell count is 12 000 20 000 with the differential count showing a slight nonspecific shift to the left All these signs are prominent immediately after an attack of paroxysmal tachycardia but the general condition usually improves amazingly soon Within minutes a life threatening situation may become normal

Discordance of the terminal oscillation was particularly striking immediately after paroxysmal tachycardia in 2 pa tients In both S T segments and T waves became normal within a few weeks after the last attack The author there fore believes that the ECG disturbances are due to tempo rary hypoxemia caused by tachycardia although Hamilton has attributed S T and T changes to heart muscle damage

Surprisingly often the Wolff Parkinson White syndrome is combined with congenital heart defects of almost every type—in the author s series in about half the patients Ven tricular septal defects are particularly frequent A previously

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ever depresses the functional capacity of the myocardium and the heart is then vulnerable to vagal stimulation Hitherto unexplained accidents during strabismus operations might conceivably be due to myocardial crises from excessive tension on the medial and/or lateral rectus oculi The response seems closely related to the oculocardiac reflex and is probably traceable to stimulation of terminal branches of the trigeminal nerve which in turn activates the vagus During strabismus operations the response is dangerously exaggerated owing to the physiologic vagotonia of children and adolescents and the effect of anesthesia on the myocardium

Some Clinical Features of Complete Heart Block George B Penton Harold Miller and Samuel A Levine[3] (Harvard Med School) reviewed 251 cases 58 due to nonacute coronary artery disease 49 to acute myocardial infarction 62 to hypertensive heart disease 21 to rheumatic heart disease 18 of undetermined etiology 16 miscellaneous and 27 due to digitalis toxicity

Of the 224 patients whose condition was unrelated to digitalis 127 (57%) were male Age when first seen varied from 10 to 85 years but 84% were aged 41 80 The youngest were in the group designated etiology undetermined Average age at death in 126 fatal cases was 63 2 years

Syncope occurred in 137 patients but none had block due to digitalis Average duration of life after first syncope was 6 9 years Palpitation was a symptom in 43 cases Congestive heart failure was present in 40% preceding accompanying or following onset of complete heart block Angina was rare during established complete block with slow ventricular rates Ventricular rate during complete heart block varied from 16 to 97

Cardiac enlargement of some degree was found in 140 but could not be detected by x ray in 47 and in 1 patient with known complete heart block for 15 years cardiac enlargement was never demonstrable Bundle branch block was noted in 122 cases in 62 on the left and in 60 on the right First or second degree atrioventricular block was present before or after complete block in 67 Ventricular tachycardia or fibrillation was observed in 15 cases

(3) C culat 13 801 8 4 J 1956

collected series of 69 cases in children showed heart defects in only 13 The syndrome was reported in 3 of 100 children with congenital heart anomalies

The syndrome requires no therapy, but paroxysmal tachycardia in the newborn or suckling is extremely serious and demands immediate medical treatment For this cedilanid (lanatoside C Sandoz) 0 04 0 06 mg/kg body weight or Acylanid® (acetyl digitoxin, Sandoz) is recommended to arrest and prevent attacks Oxygen and analeptics are also given Prognosis of the syndrome is good the final outcome depends on the accompanying heart lesion One death occurred during an attack of anoxia in an infant aged 13 weeks who had congenital anomalies of the heart and vessels including a trilocular heart and dextrocardia with agenesis of the spleen spontaneous inclusion body formation in erythrocytes and hepatomegaly

Cardiac Arrest during Strabismus Surgery Preliminary Report is presented by E John Sorenson and John E Gilmore (Santa Monica Calif) Arrhythmias of various types have been observed in every case of operation for strabismus In a consecutive unselected series of 17 cases bradycardia occurred in 16 extrasystoles in 7 and ventricular fibrillation in 1

The pattern of bradycardia was consistent In 15 cases the pulse rate before isolation of the medial or lateral rectus was 110-130 and it dropped with tension on the muscle to 40-65 In 1 pulse dropped from 72 to 25 All patients were children or adolescents and none had histories of earlier cardiac disturbances The arrhythmia occurred regardless of operative technic or premedication it developed with tension on the muscle during mobilization whether preparatory to lengthening or shortening it and terminated when tension was released The arrhythmia could be controlled by intravenous injection of atropine (1/150 gr) effectively blocking vagal stimulation Premedication with atropine was ineffective

Vagal tone reaches a peak during adolescence and early adulthood and the oculocardiac reflex is positive in 90% of children It is more easily produced under anesthesia than in the waking state A normal heart will never respond to vagal stimulation with serious symptoms Anesthesia how

(2) Am. J Ophth 41 748 752 May 1956

ventricular node and the specialized conductive tissue in the septum may occur and lead to atrioventricular conduction defects If this is true anything that reduces inflammation in the body tissues should help re establish normal conduc tion

The anti inflammatory action of adrenocortical hormones is well established Previous reports indicated that these hor mones were effective in 1 case of complete heart block fol lowing myocardial infarction and in 2 cases of idiopathic Stokes Adams attacks A recent review apparently has es tablished the fact that adrenal corticoids also exert a direct accelerating action on atrioventricular conduction since pa tients with Addison s disease exhibited a consistent statis tically significant increase in the P R interval and patients with Cushing s disease showed a shortened P R interval

Man 54 recovered from an acute posterior myocardial infarction and 6 months later had another acute infarction tentatively localized in the anterior surface and septum of the heart He was treated with morphine atropine Peritrate® and anticoagulants He responded well to therapy until 30 hours after admission when he suddenly became cyanotic had a convulsion and lost consciousness briefly Pulse was irregular 30-40/minute An ECG showed complete heart block with irregular idioventricular beats from multiple foci Oral ephedrine and subcutaneous epinephrine were ineffective Syncope and convulsions increased in frequency duration and severity until they occurred every few minutes and death appeared imminent

He was given 100 mg cortisone intramuscularly He had only one further episode of syncope soon after receiving the cortisone and in 1 hour a pulse rate of 88 was recorded An ECG taken 9 hours later showed normal auriculoventricular conduction with residual delay in intraventricular conduction with the configuration of left bundle branch block and this gradually cleared Cortisone was given in gradually decreasing doses for 4 days and then discontinued Heart block did not recur there were no further episodes of syncope and recovery was uneventful

Spontaneous reversion to sinus rhythm is considered by some to be almost the rule in patients who survive total heart block complicating myocardial infarction This was not believed to have occurred in this patient since the synco pal attacks became steadily worse and more frequent Res toration of normal atrioventricular conduction was life saving and the cortisone probably caused or greatly con tributed to that restoration Cortisone should be considered in treatment of Stokes Adams disease secondary to myo cardial infarction especially if the septal involvement is con

In 176 cases the block was permanent Single episodes were most common in the group with acute myocardial infarction Longest duration proved by ECG was 21 years though the condition was known by clinical examination to have been present for 47 years In patients who had complete heart block during acute myocardial infarction immediate mortality was high In all who survived the rhythm returned to that before infarction Complete heart block is an uncommon complication of rheumatic valvular disease

In the acute attack of complete heart block sympathomimetic amines such as epinephrine n isopropylnorepinephrine and ephedrine stimulate the rhythmic function of the heart Others such as Neo synephrine® norepinephrine methoxamine and Wyamine® have little or no effect on increasing the rhythmicity During standstill injection of epinephrine should be intracardiac If circulation is effective it can be administered parenterally and repeated frequently or constant intravenous drip employed Isuprel® is effective intravenously or by intracardiac injection Irritation of the heart with a direct needle prick may stimulate systole an external electronic pacemaker may be useful and direct massage of the heart can be lifesaving

Prevention of subsequent attacks depends on the frequency with which they occur If they are rare therapy may not be indicated If frequent sublingual isoproterenol 15 30 mg every 4 hours or ephedrine sulfate 25 50 mg 4 times daily may be valuable aqueous epinephrine 1 100 as a nebulizer spray epinephrine in oil 1 500 intramuscularly 1 to 2 times daily Isuprel® 1 200 as a nebulizer spray or atropine may be worth trial The value of thyroid therapy is uncertain Strychnine Metrazol® picrotoxin Coramine® and caffeine are of little or no value and the role of adrenal steroids needs further evaluation In patients with congestive heart failure digitalis should be employed with more careful supervision Digitalis probably has no beneficial effect in patients without objective signs of failure

Cortisone in Stokes Adams Disease Secondary to Myocardial Infarction Report of Case is presented by M D Phelps Jr and J David Lindsay Jr[4] In incomplete septal infarction or infarctions near the septum inflammation of the atrio-

(4) New Engla d J Med. 256 204 208 J 31 1957

ventricular node and the specialized conductive tissue in the septum may occur and lead to atrioventricular conduction defects If this is true anything that reduces inflammation in the body tissues should help re establish normal conduc tion

The anti inflammatory action of adrenocortical hormone is well established Previous reports indicated that these hor mones were effective in 1 case of complete heart block fol lowing myocardial infarction and in 2 cases of idiopathic Stokes Adams attacks A recent review apparently has es tablished the fact that adrenal corticoids also exert a direct accelerating action on atrioventricular conduction since pa tients with Addison s disease exhibited a consistent statis tically significant increase in the P R interval and patients with Cushing s disease showed a shortened P R interval

Man 54 recovered from an acute posterior myocardial infarction and 6 months later had another acute infarction tentatively localized in the anterior surface and septum of the heart He was treated with morphine atropine Peritrate® and anticoagulants He responded well to therapy until 30 hours after admission when he suddenly became cyanotic had a convulsion and lost consciousness briefly Pulse was irregular 30-40/minute An ECG showed complete heart block with irregular idioventricular beats from multiple foci Oral ephedrine and subcutaneous epinephrine were ineffective Syncope and convulsions increa ed in frequency duration and severity until they occurred every few minutes and death appeared imminent.

He was given 100 mg cortisone intramuscularly He had only one further episode of syncope soon after receiving the cortisone and in 1 hour a pulse rate of 88 was recorded An ECG taken 9 hours later showed normal auriculoventricular conduction with residual delay in intraventricular conduction with the configuration of left bundle branch block and this gradually cleared Cortisone was given in gradually decreasing do es for 4 days and then discontinued Heart block did not recur there were no further episodes of syncope and recovery was uneventful

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sidered due to inflammation rather than actual destruction

Quinidine as Cause of Sudden Death has long been feared as a major hazard of the drug in treatment of atrial fibrillation *George W Thomson*[5] *(Lenox Hill Hosp New York)* reviewed 611 previously uncollected cases from 12 major reports Patients were generally unselected as to underlying cause of heart disease its severity presence or absence of congestive heart failure duration of atrial fibrillation or other associated diseases

The separate risks of sudden death and embolism during quinidine therapy were appreciable Over all death rate was 3 3% (20 patients) Of 418 cases in which the incidence was evaluated clinical embolism occurred in 2 3% Death due to clinically certain cerebral embolism occurred in only 2 cases Of the 20 patients who died only 10 came to autopsy and embolism was implicated only once In most no pathologically evident cause of death could be found

Prior embolism appears to carry a negligible risk of repetition during quinidine treatment Severe organic heart disease congestive heart failure and associated grave illnesses increase the possibility of a fatal reaction Uncontrolled dosage may be a significant lethal factor Idiosyncrasies do occur with small doses of the drug and at low plasma levels which may be fatal but most important is careful control of dosage with frequent observations of the effect Mortality may be greater where no limits are set on the amount of the drug

Ventricular arrhythmias are well documented during quinidine therapy and are more frequent than cardiac arrest Coma convulsions and altered consciousness described during *aberrant ventricular rhythms are undoubtedly* related to failure to maintain adequate cardiac output and cerebral blood flow Seven such fatal reactions were reported following intravenous administration of the drug Conduction defects add to the hazard

It is generally unappreciated that quinidine may at times act as an excitant and at times as a depressant of vital centers of the central nervous system Severe depression of respiration may occur with apnea followed by circulatory collapse which can be reversed with vasopressor drugs ar

( ) Ci c lat on 14 757 764 No ember 1956

tificial respiration and central nervous system stimulants Precipitant hypotension is the chief contraindication to con tinued use of the drug These effects might be avoided by more judicious selection of patients for therapy and meticu lous supervision of all patients receiving large doses

MISCELLANEOUS

Loud Presystolic Sounds over Jugular Veins Associated with High Venous Pressure are described by William Dock[6] (State Univ of New York New York City) In some sub jects with loud presystolic sounds above the clavicle either the first sound or both normal sounds are inaudible in this area Their presence of a presystolic sound is determined by timing with the carotid pulse Presystolic jugular sounds do not occur in auricular fibrillation but loud systolic mur murs not heard over the precordium may be present with tricuspid insufficiency or even when the valve is not physio logically insufficient

The mechanism leading to a jugular presystolic sound is the same as that causing the early systolic sound over the aorta or pulmonary artery or over peripheral arteries in subjects with high stroke volume Auricular ejection into the ventricle is resisted either by high diastolic intraven tricular pressure or by tight tricuspid stenosis leading to reflux of blood into the great veins Vibration of the tensed veins causes a loud sound in the jugular areas usually pre ceding peaks of the jugular pressure and ballistocardio graphic waves A delay in the sound over the left vein com pared with the right can occasionally be noted This implies that it is in the vein itself that the sound is produced

A loud presystolic gallop sound can usually be recorded from over the jugular veins of patients with acquired or con genital heart disease when they have sinus rhythm and ele vated pressure in the right atrium The sound is maximal 0 1 0 16 second after the onset of P and absent or barely ap parent over the precordium It occurs close to the peak of the jugular *a* wave Patients with loud fourth sounds from the

(6) Am J Med 20 853-859 J 1956

jugular vein often have large presystolic headward and/or rightward gallop waves in the ballistocardiogram These presystolic phenomena are believed due to a wave of blood moving with violence centrifugally at the height of atrial systole when there is high pressure in the right ventricle at the end of diastole or when there is tricuspid stenosis

Pregnancy and Cardiac Operations Eli J Igna Marion F Detrick Conrad R Lam John W Keyes and C Paul Hodgkinson[7] (Henry Ford Hosp) report on 22 patients—16 with rheumatic mitral stenosis 3 with tetralogy of Fallot and 3 with patent ductus arteriosus—who had various cardiac or cardiovascular operations before or during pregnancy Indications for operation varied for the 3 groups In those with rheumatic mitral stenosis commissurotomy was done for actual or threatened severe deterioration of cardiac reserve

The risk is less in the early weeks of pregnancy before *work load has increased to dangerous levels* but surgery is safe at any week of pregnancy The final decision to operate depends on urgency for improving cardiac function and on the combined opinions of the cardiologist cardiac surgeon and obstetrician As a result most pregnant patients who have commissurotomy have rather urgent indications Patients with less seriously impaired hearts are usually safely carried on conservative management

Prophylactic antibiotic therapy is advantageous during labor and delivery Vaginal delivery with minimal sedation second stage forceps application early episiotomy and pudendal block anesthesia are considered good treatment Particular attention should be directed to the immediate postpartum period Tachycardia orthopnea and basal rales may herald pulmonary edema of sudden left heart failure Large volume infusions should be avoided and sodium intake restricted

Among the 3 patients with patent ductus arteriosus the duct was divided during the 20th week of pregnancy in 1 and before pregnancy in the other 2 All were converted to class I The Blalock procedure for tetralogy of Fallot was performed in 3 In 1 it was unsuccessful and 2 *subsequent* pregnancies in this patient were accompanied by critical deterioration in cardiac reserve The other 2 patients were im

(7) Am J Obst. & Gynec 71 1024 1034 M y 1956

proved to class I Among the 16 with mitral stenosis commissurotomy was performed during pregnancy in 5 and before pregnancy in 11 Two received no surgical benefit and had hysterectomy during the 2d trimester 2 others showed deterioration in cardiac reserve but were able to deliver at term by virtue of strict medical surveillance

A successful operative result usually indicated an excellent pregnancy potential A less satisfactory result usually was of prognostic value and cardiac deterioration could be predicted during pregnancy

Significance of Nonbacterial Thrombotic Endocarditis Autopsy and Clinical Study of 78 Cases found at 18 486 consecutive autopsies at the Mallory Institute of Pathology is reported by Richard A MacDonald and Stanley L Robbins[8] (Boston City Hosp)

Of the patients 40 were female and 38 male aged 18 90 Illness before death ranged from 1 day to 2 years average 3 months The commonest principal illness was cancer The commonest type of underlying heart disease was arteriosclerotic (43 cases) and next was rheumatic (14 cases) inactive and healed in each case Hypertensive heart disease was found in 6 and hypertensive arteriosclerotic in 7 patients Eight had no heart disease

The mitral valve alone was involved in 43 patients the aortic valve alone in 15 and both in 14 a combination of mitral aortic and tricuspid valves in 3 aortic and tricuspid in 1 and pulmonic and tricuspid valves alone in 1 each In each patient with nonbacterial thrombotic endocarditis the involved valve was abnormal

In 11 patients there was clinical and pathologic evidence of multiple embolization of organs and no other source for emboli was found The infarctions were of such age histologically as to indicate they had been present before death and did not occur as a terminal event

A pre existing focal nonspecific valvular deformity appears to be definitely related to the subsequent formation of a thrombus At autopsy focal valvular deformities are seen in many persons but nonbacterial thrombotic endocarditis in only a few The other necessary factors are unknown There was no evidence for considering these vegetations to

(8) A I Med. 46 255 273 F bruary 1957

be sterilized bacterial endocarditis The anatomic findings were no different in the patients who had received antibiotics than in those who had not

If the chief clinical picture is one of multiple embolization of organs the diagnosis may be made before death In a patient with cardiac decompensation the important distinction is between bacterial endocarditis and mural thrombi of cardiac chambers Once the diagnosis is made there is no specific therapy The chief therapeutic value of clinical recognition is in differentiating embolic cerebral vascular disease from hemorrhage and thrombosis and in directing attention to associated and perhaps causative conditions

Cardiac Amyloidosis Primary systemic amyloidosis is less rare than generally supposed Heart failure is present in more than half the cases and is now accepted as the most important single feature Robert Benson and J F Smith[9] (London Hosp) describe clinical and pathologic findings in 5 cases with cardiac symptoms

Dyspnea on exertion was the main complaint of each patient and was the initial symptom in all but 1 who had paroxysmal tachycardia Anasarca was present in 4 Anginal pain was absent and is almost unknown in cardiac amyloidosis A variable degree of generalized cardiac enlargement was always found Cardioscopy showed sufficiently diminished pulsations of the heart in 1 patient to suggest constrictive pericardial disease Murmurs were absent Hypotension was noted in 3 patients The ECG showed low voltage diphasic T waves and right bundle block was present in 2

There was albuminuria in 3 cases None showed any of the noncardiac manifestations so often described in primary amyloidosis Slight induration of the tongue was noted at autopsy in 1 patient Enlargement of the liver and spleen from amyloid deposition is atypical Each of these patients had an enlarged liver shown at autopsy to be due to heart failure In none was the spleen palpable but one appeared moderately enlarged from amyloid deposition at autopsy

In 4 of the 5 cases involvement of the myocardium was *conspicuous and sufficient to explain cardiac* failure through mechanical interference with normal heart action as in constrictive pericardial disease In 1 case it appeared as a form

(9) Brit H art J 18 529 543 O tober 1956

of endarteritis fibrosa in the pulmonary circulation The de posits of amyloid in the walls of blood vessels were extensive but variable in the interstitial tissue of the heart in smooth muscle organs of the alimentary tract and occasionally in nerves and voluntary muscles There was an overlap of dis tribution with that found in secondary amyloidosis Of all criteria given for diagnosis of primary amyloidosis absence of pre existing or etiologic disease is the only constant clin ical and pathologic finding

Recognition during life is difficult but the diagnosis should be considered when otherwise unexplained heart failure es pecially with normal rhythm and hypotension is accompa nied by an ECG showing equivocal changes in the T wave or defect in conduction Cardiac amyloidosis may simulate con strictive pericardial disease

Familial Hemachromatosis Cardiac Decompensation and Treatment by Blood Letting R Kappeler[1] (Bern) reports on a family in which 3 brothers had hemochromatosis 2 died of the disease at ages 42 and 44—the first in cardiac failure and the second in comatose collapse without diabetes and ic terus The other aged 52 had hemochromatosis without dia betes and was symptom free and able to work He was satis factorily treated by blood letting for 13 months

A fourth brother had had hepatitis with icterus 2 years previously with a subsequent temporary increase in level of serum iron but was not believed to have hemochromatosis Two sisters were well with normal serum iron levels One other brother died of bronchial carcinoma and another was in good health Six of 7 offspring of the 3 brothers with he mochromatosis aged 11 22 were examined 4 showed sur prisingly high levels of serum iron—166 183 202 and 228 μg /100 ml This finding may represent an early sign of hemochromatosis

In the first patient fairly acute heart failure began with predominantly right sided insufficiency only temporarily controllable about 2 months before death On hospitaliza tion 8 days before death circulation was once more nearly compensated by cardiac therapy but the heart was for the first time bilaterally enlarged The ECG demonstrated pro nounced myocardial damage Tachycardia and auricular fi

(1) Schwei m d W hsch 86 477-481 1956

brillation accompanied by extrasystoles appeared and *promptly led to irreversible decompensation* resistant to all treatment which progressed to death within a few days

Many authors have observed heart involvement in hemochromatosis In a series of 65 patients, heart failure caused death in 8 aged 33-49 Cardiac failure has appeared also in patients aged 17 20 Left sided failure precedes the later predominantly right heart deficiency by only a few weeks in some instances decompensation may develop fully within a few days Clinical symptoms include tachycardia hypotension cardiac dilatation low tonus gallop rhythm systolic murmurs and various rhythmic disturbances especially auricular fibrillation and extrasystole Heart decompensation occasionally may be the first subjective symptom of hemochromatosis Anginal symptoms and myocardial infarct are rare but milder cardiac disturbances are frequent (20-40%) Characteristically with rare exceptions the heart responds to treatment only temporarily Cardiac insufficiency usually lasts several months but sometimes only a few weeks In favorable instances survival may be 20 months to 2 years and even as long as 6 years

The ECG changes which may be observed before symptoms of cardiac decompensation appear are nonspecific and involve principally the T wave which may be flattened biphasic or negative with changes most common near the base Extrasystoles are frequent and with polytopic localization are an unfavorable prognostic sign Other ECG changes such as P Q lengthening sinus auricular blocking Wenckebach s period various types of block etc are observed less often

Autopsies have shown no direct correlation between cardiac decompensation and degree of myocardial pigmentation Several new hypotheses and investigations offer a fresh approach to the problem of cardiac failure in hemochromatosis One attractive theory is that the mechanism responsible for the rapidly evolving heart decompensation in hemochromatosis which may be accompanied by circulatory collapse *is analogous to that of therapy resistant* shock caused by ferritin a vasodepressor

In familial hemochromatosis there apparently is a congenital disturbance of iron metabolism since abnormally high

serum iron levels were found in 4 adolescent and young adult sons of the author s patients Nevertheless it is questionable whether this disturbance is a factor in isolated cases

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DISORDERS OF THE PULMONARY CIRCULATION

Unexplained Pulmonary Hypertension Geoffrey Wade and John Ball[2] (Manchester England Royal Infirm) present 10 cases 7 studied histologically The cases are not homogeneous clinically or pathologically and the two main mechanisms appear to be a functional contraction of the terminal muscular arteries and abnormal bronchopulmonary anastomotic channels

Dyspnea an invariable symptom differs from the usual type in cardiac or pulmonary disease It is exertional only and is often associated with fatigue substernal oppression faintness or syncope Orthopnea is never observed and in later stages the contrast between the distress on effort and the well being at rest is striking Pulmonary distensibility and viscous resistance are normal Cardiac output is limited and may cause functional coronary insufficiency and angina Effort syncope may occur Hemoptysis is rare and apparently due to hemorrhage from dilated vessels in the submucous layer of the bronchi

Physical findings indicate pulmonary hypertension diffuse cardiac impulse triple rhythm accentuation of the pulmonary second sound pulmonary systolic murmur or a Graham Steell murmur Cyanosis is present in about half the reported cases Arterial oxygen saturation below 87% has never been reported

Radiologic findings are characteristic of pulmonary arterial hypertension with a normal capillary bed enlargement of the right ventricle dilatation of the proximal portion of the pulmonary arterial tree narrowing of the distal branches and normal peripheral lung fields Hilar dance an indication of increased flow is not seen on fluoroscopy The ECG invariably shows right ventricular enlargement usually extreme

(2) Quart. J Med 26 83 119 J ry 1957

Five patients presented a fairly uniform picture of progressive symptoms ascribable to low cardiac output and died of right ventricular failure in 10 30 months The physical findings were only those of pulmonary hypertension This almost malignant course is typical of described cases of primary pulmonary hypertension Such patients may have an arteritis confined to the lungs but usually they do not The increased pulmonary vascular resistance is due to a primary contraction of terminal muscular arteries Intimal fibroelastosis *and pulmonary arterial thromboses when present* are secondary Treatment is disappointing Vasodilators are of no value Steroids may help if the difficulty is due to arteritis

In another group pulmonary hypertension is due to involvement of the lungs in an indeterminate generalized arteritis Patients in addition to symptoms and signs of primary pulmonary hypertension have signs of digital arterial disease These cases may be related to progressive systemic sclerosis In this group steroids seem the only hope although *experience has not been encouraging*

In a third group with abnormal bronchopulmonary communications the natural history may be long hemoptysis common and cyanosis and polycythemia more pronounced Such cases are difficult if not impossible to distinguish from congenital heart disease with a left to right shunt and complicating pulmonary hypertension The anastomotic vessels probably cause the hypertension

Unless characterized by bronchopulmonary anastomotic vessels patients with disease confined to the lungs present a fairly constant clinical syndrome of circulatory inadequacy without congestion of the lungs and signs of pulmonary hypertension possibly followed by congestive failure The syndrome is easily recognizable if the possibility is considered

Any procedure which may lessen cardiac efficiency is not well tolerated Deaths have been reported after simple exercise tests and several after cardiac catheterization Hypotensive drugs are of no benefit and sympathectomy should not be attempted No effective treatment is known for patients with abnormal bronchopulmonary communications Only those with arteritis of the pulmonary vessels may possibly be helped by steroids but in those so treated results have been disappointing

► [This and the several subsequent communications emphasize the frequency and importance of cor pulmonale. This disorder now probably ranks as the fourth or fifth commonest cause of congestive heart failure. In most instances it is secondary to detectable disease of the lungs but an increasing number of patients are being encountered in whom the pulmonary arterial disease appears to be primary. When such a patient happens to have a presystolic or protodiastolic right ventricular gallop the condition may be confused with mitral stenosis and a number of unnecessary exploration of the mitral valve have been done. This error may be minimized by careful auscultatory distinction between rumbles and gallops. Other helpful points are the absence of evidence of pulmonary congestion and edema in patients with cor pulmonale and the presence of a brief tall spiked P wave in the electrocardiogram as contrasted with the broader and notched P wave in patients with mitral stenosis.—Ed.]

Clinical Physiologic and Pathologic Considerations in Patients with Idiopathic Pulmonary Hypertension For classification of this condition the mitral valve must be normal and the left ventricle competent and there must be no evidence for an abnormal communication between the lesser and greater circulations and no diseases of the pulmonary parenchyma. However even after the most careful clinical and physiologic studies unsuspected malformations of which pulmonary hypertension is a functional accompaniment may sometimes be found at autopsy in a case that was designated as one of idiopathic pulmonary hypertension. Ten patients with pulmonary hypertension are reported by John T Shepherd Jesse E Edwards Howard B Burchell H J C Swan and Earl H Wood[3] (Mayo Clinic and Found.) In 4 a right to left shunt was present at the atrial level. An atrial septal defect of moderate size was found at autopsy in 1.

Age of the patients was 24-46 years and 9 were women. Complaints were primarily of increasing weakness and dyspnea on exertion from 1 month to 18 years. Seven had had one or more attacks of syncope on exertion. 5 had had thoracic pain on effort resembling angina pectoris. No patient had orthopnea paroxysmal dyspnea or hemoptysis. The characteristic physical finding in each was an accentuated second sound. Four had a pulmonary diastolic murmur. The ECG showed right ventricular hypertrophy in all cases confirmed by x rays which also showed a prominent arterial segment. X rays of peripheral pulmonary fields showed normal or diminished vascular shadows and no parenchymal disease. At cardiac catheterization the pulmonary arterial pressure was greatly increased wedge pressure was within

(3) Brit. H rt J 19 70-8 J uary 1957

normal limits and pressure in the right atrium was raised in 6 Of the 4 with right to left shunts, 3 had normal right atrial pressures Pulmonary flow was always below normal and total pulmonary resistance extremely high Obstruction to flow was proximal to the pulmonary capillary bed

The pathology found at autopsy does not permit firm conclusions as to the cause In 1 of the 3 autopsies the lesions were consistent with pulmonary embolism or thrombosis although no recognized cause for either existed In another medial hypertrophy of the muscular arteries was striking perhaps a persistence of fetal characteristics of pulmonary arteries In the third the lesions may have been thrombo embolic but were not definitely so

An arteriole that seems normal at one level may be entirely occluded by a lesion at another This may explain some previous opinions that the number of occluded arterioles seemed inadequate to explain the degree of pulmonary pressure At certain levels an artery may be occluded by a bland thrombus not associated with changes in the arterial wall but at other levels which are occluded there may be a necrotizing process in the wall Organic changes in the pulmonary vessels appear sufficient to explain the pulmonary hypertension

Primary Pulmonary Hypertension Review of Literature and Results of Cardiac Catheterization in 10 Patients The *frequency with which this disease occurs is difficult to evaluate* but it probably is not as rare as previously considered Ten patients are reported by Don W Chapman Jack P Abbott and Joseph Latson[4] (Baylor Univ)

Exertional shortness of breath was present in each case but dyspnea at rest was a late symptom Only 1 patient had orthopnea 6 had at least one episode of hemoptysis and 6 had at least mild cyanosis Four patients had syncope related to exertion Coughing was noted in all but 1 varying from an occasional dry cough to severe episodic bouts productive of frothy purulent or bloody sputum Chest pain was present in 4 and severe in 2 Pain was predominantly substernal and in some radiated down both arms on *exertion* at times it could be relieved by nitroglycerin

(4) C culat on 15 35-46 J ry 1957

All but 2 patients were slender and undernourished None had systemic hypertension One had minimal clubbing of the fingers The lungs were usually clear on physical examination although 1 patient had bilateral crepitant rales and 1 had pleural effusion All had right ventricular overactivity The heart was enlarged to the left in all but 1 and to the right in 5 patients Thrills were palpable along the left sternal border in the 3d and 4th interspaces in 2 patients All had regular sinus rhythm pulse rates between 70 and 130/minute and P was louder than A in all but 1 Eight patients had murmurs predominantly pulmonary systolic murmurs although 2 had diastolic murmurs Two patients had an apical systolic murmur and 2 had questionable apical presystolic murmurs In 6 the liver was enlarged and tender

Teleroentgenograms and fluoroscopy revealed right ventricular hypertrophy prominent pulmonary arterial segments and frequently dilated pulmonary trees well out in the lung parenchyma Some had marked pulsations in the pulmonary hilar vessels There were no parenchymal lesions or left atrial enlargement The ECG s showed right ventricular hypertrophy in 9 of the 10 cases and 2 far advanced cases had ischemic T wave changes Routine laboratory procedures were of little diagnostic importance Two patients had an elevated erythrocyte count and hemoglobin level In the 9 patients catheterized high right ventricular and pulmonary arterial pressures were found Pulmonary capillary pressures in 3 were normal This may be important diagnostically in differentiation from secondary pulmonary hypertension in which this pressure is elevated

At autopsy characteristic findings were right ventricular hypertrophy with areas of focal fibrosis without valvular or endocardial abnormalities Histologically the lumens of the middle sized and smaller pulmonary arteries and arterioles were strikingly smaller Occasionally soft small yellow raised atheromatous plaques were found in the major pulmonary arteries In middle sized and smaller arteries and arterioles the depth of subendothelial space was much increased because of many lipid laden mesothelial cells The intima was usually intact but frequently the lumens of small vessels were completely obliterated by organized thrombi

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(4) Circulation 15 35-46 January 1957

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and subintimal fibrosis Musculature of the smaller arteries and arterioles was distinctly thickened from increase in fibrous connective tissue without increase in muscle

No known therapy is beneficial Prognosis is usually poor with an unrelenting downhill course of right ventricular failure ending in death from 5 months to 5 years after onset of symptoms However one patient has had exertional dyspnea for 12 years and is still fairly well without right heart failure

Massive Thrombotic Occlusion of Large Pulmonary Arteries is seldom considered in differential diagnosis of obscure cases of right sided heart failure although over 200 cases have been reported It is usually described as associated with other diseases notably pulmonary tuberculosis carcinoma of the lung and congenital or acquired heart disease but it may also occur as a primary lesion K P Ball J F Goodwin and C V Harrison[5] (London) present 23 cases 9 seen during life and 3 correctly diagnosed ante mortem In 4 patients there was no associated disease although 3 had a generalized thromboembolic tendency of unknown etiology

The most common symptom was dyspnea Symptoms compatible with pulmonary infarction were present in 11 of the 23 patients fainting was notable in 3 In most cases symptoms of the associated or underlying disease overshadowed any due to the thrombotic lesion Several patients died in coma

Physical findings were right ventricular hypertrophy although in several this was due to mitral stenosis an accentuated pulmonary second sound and an abnormal central venous pulse Congestive cardiac failure was noted in 10 patients Only 3 had signs suggesting peripheral venous thrombosis In 14 patients with adequate chest films right ventricular and pulmonary artery enlargement was a constant feature and the lung fields appeared underfilled in 3 Restricted pulsations of the main arteries was striking in 2 patients Of 12 patients ECGs showed right ventricular hypertrophy in 8 and right atrial hypertrophy in 4 No abnormalities of the right heart were seen in 4 Thrombosis was considered secondary to embolism in most but appeared

(5) Circul tion 14 766-783 November 1956

to have arisen in situ in a few Pulmonary infarction was frequent but not invariable Death was gradual in 18 and sudden in 5

Symptoms of thrombotic occlusion are insidious and are generally those of right heart failure and low cardiac output Dyspnea occurs in most patients hemoptysis apprehension cough mental confusion and substernal pain are common Cyanosis apparently peripheral is frequent Signs of pulmonary artery hypertension and right ventricular failure are common Pulmonary artery thrombosis should be considered when a patient presents unexplained congestive cardiac failure dyspnea fainting repeated episodes of pulmonary infarction or chest pain

Treatment has been unsuccessful probably because diagnosis has not been made early Prolonged anticoagulant therapy offers the only hope of preventing extension of the thrombus Ligation of the inferior vena cava might be required if the thrombosis is secondary to repeated pulmonary emboli from thrombosis of the leg veins and cannot be controlled by anticoagulants

Relation of Pectus Excavatum to Heart Disease Pectus excavatum (funnel chest or trichterbrust) is a congenital thoracic deformity consisting of dorsal displacement of the sternum with costochondral concavity from side to side and from above downward Secondary changes may involve the vertebral column paravertebral musculature and thoracic viscera The volume of the thoracic cavity is decreased with variable degrees of compression and rotation of the lungs heart mediastinum and great vessels

Fred W Wachtel Mark M Ravitch and Arthur Grishman[6] (Mount Sinai Hosp New York) report that their experience covers 50 patients who were operated on of whom 43 were children the youngest aged 3 months and 7 adults the oldest 38 years Results in terms of thoracic reconstruction improvement in general well being appetite weight gain and exercise tolerance have been uniformly satisfactory The present report concerns particularly 13 patients studied since 1952 11 of whom were operated on Symptoms included regurgitation of food in the younger patients dyspnea on exertion decreased exercise tolerance and palpita

(6) Am. H rt J 52 121 137 J ly 1956

tions No patient had chest pain cough paroxysmal dyspnea or peripheral edema Funnel chest deformity was obvious in all and many had systolic murmurs along the left sternal border None had evidence of congestive heart failure or lung disease The most conspicuous changes on chest x rays were extension of the cardiac silhouette to the left

The ECG in each case showed sinus rhythm without extrasystoles In several there was a tendency to right axis deviation The QRS was normal in each Vectorcardiography showed no intraventricular conduction defect or myocardial damage The rSr or rSR pattern observed in V_1 was considered a variation of normal and not an indication of incomplete right bundle branch block

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This deformity can be corrected by surgery with good physiologic and cosmetic results For these reasons and because the deformity is congenital and unpredictably progressive surgery should be recommended for infants with marked deformity infants with observed progression of the deformity children and young adults with marked deformity and adults with symptoms

Peculiar Type of Cardiopulmonary Failure Associated with Obesity Several recent reports have appeared of patients with extreme obesity associated with cyanosis polycythemia hypercapnia and right sided heart failure without recognizable heart or lung disease Two cases are reported by Douglas Carroll[7] (Johns Hopkins Univ)

Both patients had been obese for several years before heart failure developed None of the common causes of heart failure could be demonstrated in either Vital capacity was reduced with no suggestion of emphysema Anoxemia and hypercapnia were severe during heart failure but tended to

( ) Am J Med 21 819 824 N mbe 1956

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Certain physiologic abnormalities secondary to obesity are postulated which may have led to the clinical picture Both patients scarcely moved their chest walls with deep respiration perhaps due to the heavy fat pads which immobilized the rib cage Breathing was predominantly abdominal Fluoroscopy showed normal diaphragmatic motion and normal maximal breathing capacity when 1 patient was completely compensated but this was brought out only by intensive urging over short periods Breathing apparently required a greater expenditure of energy than in normal subjects

Breathing was inefficient as shown by the tendency to hypercapnia The severe alveolar hypoventilation lowered the alveolar oxygen tension and arterial blood oxyhemoglobin saturation The increased pulmonary artery pressure may be associated with a low alveolar oxygen tension Poor distribution of the inspired air was implied by the presence of a physiologic shunt in both patients The arterial oxyhemoglobin unsaturation in turn caused polycythemia and increased blood volume The heart was required to pump more blood against an increased pulmonary artery pressure with a less efficient oxygen supply Under these conditions right ventricular hypertrophy ECG changes and right sided failure were not unexpected

Apparently the amount of work necessary to keep the carbon dioxide pressure normal is so great that the carbon dioxide level is allowed to rise in preference to expending the excess energy Such situations also exist in the hypercapnia of obstructive emphysema respiratory poliomyelitis bilateral fibrous pleurisy and in kyphoscoliosis without emphysema

Management of Cor Pulmonale in Chronic Pulmonary Disease with Particular Reference to Associated Disturbances in Pulmonary Circulation is reviewed by Alfred P Fishman and Dickinson W Richards[8] (Columbia Univ) Cor pulmonale designates dilatation hypertrophy or failure of a heart secondary to intrinsic disease of the lungs and confined largely or entirely to the right heart The definition

(8) Am Heart J 52 149 160 July 1956

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excludes such changes which are secondary to diseases in the left heart

The common denominator in the evolution of cor pulmonale since there is no intrinsic underlying heart disease is an increase in work of the right heart Right heart strain and failure are generally late developments in the natural history of lung disease They are common in chronic pulmonary emphysema chronic bronchitis asthmatic or bullous emphysema silicosis or silicotuberculosis fibrotic tuberculosis alveolar capillary block severe kyphoscoliosis multiple pulmonary emboli and primary pulmonary hypertension

Moderate or even considerable restriction of pulmonary function—restrictive obstructive or alveolar respiratory—may exist with little or no increase in pulmonary arterial pressures and no evidence of cor pulmonale As pulmonary vascular resistance increases because of progression of parenchymal or vascular disease pulmonary hypertension becomes manifest during exercise and in time, may even be present at rest Evidences of cor pulmonale generally do not appear until pulmonary artery pressure exceeds twice normal In a patient with chronic lung disease cor pulmonale is suggested by the presence on x ray of an enlarged right ventricle and a prominent dilated pulmonary artery as well as ECG evidence of marked right axis shift right ventricular hypertrophy or incomplete right bundle branch block An accentuated second pulmonic sound often associated with pulmonary hypertension is not pathognomonic of cor pulmonale Earliest evidence of incipient cor pulmonale can be obtained only by cardiac catheterization The heart maintains a normal output at rest with a normal increment in flow during exercise The first evidence of right heart strain is an increase in right ventricular end diastolic pressure during exercise of 7 10 mm Hg reflecting inadequate ventricular emptying

Onset of right heart failure may be insidious clinically with gradually increasing edema of ankles and legs over days and weeks or may be sudden during an acute respiratory infection The etiology of heart failure is pulmonary when arterial oxygen saturation is below 85% polycythemia marked and carbon dioxide increased Gallop rhythm is common but hydrothorax is rare

In patients with critically diminished p[illegible]ry vascu

lar bed increased pulmonary vascular resistance is more or less fixed and irreversible and only partial restoration of cardiac function can be anticipated First attention is directed to treating the pulmonary disease with antibiotics broncho dilators antitussives etc In early stages oxygen therapy can be used freely without risk of carbon dioxide retention Respirators will often be helpful in bullous emphysema Cardiac therapy includes digitalis low salt regimen and diuretics Phlebotomy of 500 cc is valuable when the liver is enlarged and hematocrit elevated For patients with persistently elevated carbon dioxide Diamox® may be used in doses of 250 or 500 mg daily

Patients with impaired alveolar capillary diffusion of oxygen may receive the same general treatment In advanced cases oxygen therapy usually has to be given continuously and in high concentrations In granulomatoses steroids are important They may be dramatically successful without effect or even harmful

Patients whose primary difficulty is in alveolar ventilation and perfusion have a history of usually long standing asthma and obstructive dyspnea The spirogram suggests severe obstruction to expiration and residual volumes are large The outstanding physiologic disturbance is poor aeration of perfused alveoli profound arterial hypoxemia and carbon dioxide retention resulting in polycythemia and increased blood volume Pulmonary function should be treated Restlessness and even belligerence may reflect carbon dioxide retention and sedatives must be avoided Air passages must be opened and kept clear The bronchodilator aerosols 5 10 drops vaporized from an oxygen tank or motor blower and inhaled for 10 minutes systematically four times daily should be a basic routine After each treatment the patient should cough and raise sputum Steroids in small doses may help Oxygen must be given cautiously Intermittent positive pressure and artificial respirators may be required In addition to general cardiotonic measures of digitalis low sodium intake and mercurial diuretics several phlebotomies within 2 or 3 weeks will be needed to reduce the blood volume to normal as well as repeated phlebotomies at 1 or 2 month intervals to prevent hypervolemia Diamox® is also useful as a continuous medication

By careful management these patients can be carried

fairly successfully for 5 10 periods though eventually they become cardiopulmonary cripples wholly dependent on respiratory aids

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CEREBRAL VASCULAR DISORDERS

Acute Spontaneous Cerebral Vascular Accidents in Young Normotensive Adults Cerebral vascular disease reaches its peak incidence in later life If it occurs in a normotensive person under 40 the etiologic diagnosis becomes important Bertram E Sprofkin and Hubert H Blakey[9] (Vanderbilt Univ) report 18 cases The diagnoses included disseminated lupus erythematosus scleroderma thromboangiitis obliterans thrombotic thrombocytopenic purpura fibrinogenopenia of pregnancy postmeasles hemiplegia subacute bacterial endocarditis angiomatous malformation postpartal cerebral venous thrombosis spontaneous subcortical hematoma syphilis and cerebral thrombosis of unknown cause Premature arteriosclerotic vascular changes constitute the most important pathogenetic factor in this type of accident

Disseminated lupus erythematosus polyarteritis nodosa dermatomyositis and scleroderma have certain histopathologic features in common involving the collagenous intercellular material which swells and exhibits a fibrinoid change Affected areas are infiltrated by polymorphonuclear leukocytes and round cells Eosinophils may be present *No consistent neurologic syndrome has been defined for* either lupus erythematosus or polyarteritis nodosa because of the variable and widespread pathology

Many blood dyscrasias may be responsible for cerebral hemorrhage and thrombosis including the purpuras hemophilia fibrinogenopenia and hypoprothrombinemia Sickle cell disease and polycythemia vera commonly lead to thromboses Fibrinogenopenia during pregnancy is an uncommon cause of intracranial hemorrhage Cerebral embolism due to subacute bacterial endocarditis is no diagnostic problem if the possibility is considered The increasing use of intracranial angiography during the past decade has delineated the role of saccular aneurysms and angiomatous malfor

(9) A.M A A ch I t Med 96 617-630 Novembe 1956

mations in production of apoplectic neurologic syndromes

Caroticovertebral Stenosis Recognition of occlusion of the cervical portion of the carotid artery is a major advance in the study of cerebrovascular diseases Atheroma in this site may explain many cases of cerebral infarction which have shown no occlusion of intracranial vessels However occlusion of the carotid artery may be present without any symptoms or signs or infarction of the brain It may mimic the clinical picture of middle cerebral artery thrombosis or may present as a steadily progressive intracranial lesion These variations are probably due to changes in the vertebral artery which often accompany atheroma in the carotid and probably play an integral role in certain of the syndromes Atheromas are so often present in both vessels that the term caroticovertebral stenosis has been suggested

Edward C Hutchinson and Peter O Yates[1] (Manchester England) injected radiopaque gelatin through the carotid and vertebral arteries at autopsy at a pressure simulating systolic blood pressure during life in 83 patients who had had clinical evidence of cerebral vascular disease The carotid and vertebral arteries and brain were removed fixed and examined

Infarction of the brain was commonly found without occlusion of the intracranial vessels but in each case the clinical phenomenon and distribution of infarcts could be explained when the carotid and vertebral arteries were examined throughout their length Infarcts were frequent in the hindbrain particularly the cerebellum most commonly in the area supplied by the superior cerebellar artery near the junction with the territory of the inferior cerebellar artery Within the territory of the middle cerebral arteries the infarction was often incomplete

Unilateral carotid artery atheroma in 10 patients caused no cerebral infarction and in each the vertebral arteries were patent The commonest condition (23 cases) was that in which all major vessels of the neck were affected by atheroma Slowly progressive cerebral disease should be regarded as due to progressive diminution of total cerebral blood flow

Stenosis of the cervical portion of the vertebral arteries is important in the clinical picture previously attributed to occlusion of the internal carotid arteries alone Caroticover

(1) La t 1 8 Jan 5 1957

tebral stenosis is a more appropriate title for this syndrome The severity of disease of the extracranial arteries is surprising when contrasted to that of the intracranial cerebral arteries Intracranial vessels may be normal Perhaps in the future surgical replacement of diseased segments may be possible and total blood flow to the brain improved

Eyeball Bruits Physicians seldom employ auscultation over the face and head areas More frequent auscultation may reveal a bruit as a sign in some relatively common pathologic entities Jonas H Cohen and Stanley Miller (Baltimore) discovered 7 such instances in 2 years at a general hospital

Bilateral eyeball bruits have been observed in hyperthyroidism and severe anemias Unilateral bruit has been noted secondary to trauma from pressure of a mass on a blood vessel and in intermittent exophthalmos One of the commonest causes is aneurysmal angioma and other frequent causes are *thrombosis and arteriosclerosis of the internal* carotid artery In the 7 cases reported bruits were either localized at or heard most loudly over one eyeball Auscultation of the head should routinely include application of the stethoscope to the eye itself especially in cases of neurologic and circulatory diseases in which no bruit is audible over the cranium

The quality of the bruits heard was similar in all cases although intensity varied from patient to patient and from time to time in the same patient All were synchronous with *the heart beat and systolic The sound was soft and blowing* They disappeared with pressure on the ipsilateral common carotid artery except in cases of anemia

Arteriosclerosis of the internal carotid artery causing angulation of the vessel and narrowing finally culminating in complete occlusion or thrombosis may explain the unilateral location the transiency and the gradual disappearance of the bruit as complete thrombosis and/or recanalization occurred

Of the 7 patients who had an eyeball bruit 2 were proved and 1 suspected to have arteriosclerotic narrowing of the carotid siphon One was caused by internal carotid artery *thrombosis in the cavernous portion 1 was due to* hemangioma and 2 were secondary to profound anemia In 2 with

(2) New England J Med. 255 459-464 Sept. 6 1956

anemia and 1 with hemangioma bruits were heard bilaterally the other 4 patients had unilateral eyeball bruits In 6 cases the bruit was confined to the eyeball itself

Current Indications for Use of Anticoagulant Drugs in Cerebrovascular Disease The danger of intracerebral hemorrhage and causation of gross bleeding into an infarct require great caution in the use of anticoagulants in cerebrovascular disease According to Robert G Siekert Clark H Millikan and Richard M Shick[3] (Mayo Clinic) indications for anticoagulant therapy in cerebrovascular disease include intermittent insufficiency of the basilar arterial system or internal carotid system thrombosis in the basilar arterial system recurrent cerebral emboli associated with a likely cardiac source and possibly recurrent cerebral thromboses The authors treated 22 patients with intermittent insufficiency of the basilar arterial and 11 with insufficiency of the internal carotid system The attack promptly abated after effective anticoagulant levels were obtained About 50 patients with thrombosis in the basilar arterial system received anticoagulant drugs There was a striking decrease in mortality and surprising improvement in the neurologic abnormalities The mortality among patients receiving anticoagulant therapy was 14% whereas in a control group of patients receiving no such therapy it was 43%

In instances in which rapid action was required heparin was used early Otherwise Tromexan® and Dicumarol® were used the latter for long term management Usually use of the anticoagulants for an indefinite period was suggested

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PERIPHERAL VASCULAR DISEASE

Visualization of Aortic and Arterial Occlusion by Percutaneous Puncture or Catheterization of Peripheral Arteries Sven I Seldinger[4] (Karolinska Hosp Stockholm) performs percutaneous catheterization of arteries by introducing a flexible metal guide into the artery through the needle removing the needle and then passing a catheter the same size or larger than the bore of the needle over the guide

(3) Circulation 13 725 728, May 1956
(4) Angiology 8 73 86 February 1957

Aortic catheterization has been done via percutaneous puncture of the brachial artery The catheter is advanced under fluoroscopic control with the nonopaque tip visualized by the thin flexible metal guide which should reach its tip In all cases of possible abdominal aortic occlusion a trial injection with a small quantity of dilute contrast medium is important Excessive concentrations of dye in the superior mesenteric or renal arteries may cause death

Puncture of the subclavian artery is the technic of choice for demonstrating arterial occlusion in the shoulder axillary and brachial regions Pulsations of the artery can usually be palpated behind the middle of the clavicle

In puncture of the brachial artery the artery proximal to the site of injection should not be compressed If the needle is directed distally and surrounded by a contracted artery contrast medium will be injected into a bloodless area and ischemia may occur unless there are enough collateral vessels

Unilateral occlusion of the iliac artery is easily shown by percutaneous catheterization of the femoral artery punctured close to the inguinal ligament The catheter tip should be advanced as close to the bifurcation as possible A tourniquet applied just below the puncture increases the amount of contrast medium entering the desired artery In more than 500 iliac catheterizations no signs of embolus were observed If a fresh floating and unorganized thrombus is suspected catheterization of the aorta should be done via the brachial artery

For demonstrating arterial occlusion in the thigh and proximal part of the calf the same type of puncture is used directed proximally in this type also The catheter can be advanced to the popliteal artery if better visualization of the calf and foot vessels is desired

Further Observations on Takayashu s Syndrome are presented by Erik Ask Upmark and Carl Martin Fajers[5] In essence this is the aortic arch syndrome with obliteration of the big arteries arising from its convexity Characteristic features are malnutrition of the cranial half of the body development of collaterals from the caudal half and increased blood pressure in the lower half The aortic arch syndrome

(5) Acta med scand 155 275 291 1956

may be induced by syphilitic aortitis as well as by Taka yashu s syndrome in which case serology is positive sex incidence is 1 1 and it tends to occur in middle aged per ons

Takayashu s syndrome is predominantly a disease of women apt to occur in ages 15-45 Anatomically the lesion is compatible with primary arteritis Some evidence indicates a rheumatic or rheumatoid origin The lesion seems to be re lated histologically to the temporal arteritis of Horton The most important effect of the lesion is cerebral malnutrition

Diagnosis should be established with certainty particu larly ruling out syphilis and the site and extent of vascular obstruction outlined by arteriography If possible circula tion should be surgically restored If not steroids should be tried

Woman 40 had effort induced pains in the arms reduced visual acuity and syncope on rising from a recumbent position particularly during menses for 5 years For several months she had signs of cardiac insufficiency with tachycardia and angina dyspnea on effort nocturnal dyspnea and reduced urine output.

On examination there were no radial cubital or right carotid artery pulses There were questionable pulsations in the left carotid. Abdominal aorta femoral arteries and dorsalis pedis were all pulsat ing well Blood pressure was unobtainable in the arms and elevated in the legs The heart was enlarged and ophthalmologic and neuro-logic examinations were normal Renal insufficiency gradually in creased to uremia pulmonary edema supervened and she died

At autopsy bilateral microgyria was found in the occipital and frontal lobes The heart was dilated and hypertrophied There was an arteritis involving all layers of the affected arteries and severe arteriosclerosis particularly in the abdominal aorta but sparing the arteries distal to the obstructions The involved arteries were the brachiocephalic trunk right subclavian right axillary vertebral right and left common carotid and left subclavian The descending thoracic aorta had a thick wall but arteriosclerosis was least pro-nounced in this region The intercostal arteries were wide and tor tuous

Coarctation of the Abdominal Aorta Review of Litera ture A case is reported by Thomas W Inmon and Byron E Pollock[6] (Letterman Army Hosp) This is a rare condition previously reported only 13 times Average age at the time of diagnosis was 32 years Neither sex nor race appears to be a factor In 10 cases the site of coarctation was at or below the renal arteries Presence of demonstrable collateral arterial circulation in the abdominal wall favors diagnosis of coarc

(6) Am Heart J 56 314 320 A gust, 1956

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(5) A ta med sca d a 155 275 291 1956

Most clinical and pathologic information on healed dis secting aneurysms comes from isolated case reports In a re view of 79 reported examples 16 patients were found to have survived longer than 1 year and re entry of the dissection into the original lumen was apparently a prerequisite for survival When re entry did not occur 96% of patients died within 5 weeks Re entry into the original lumen is most likely when the dissection reaches some obstruction due to increased pressure within the aneurysmal sac The most com mon causes of death in chronic dissecting aneurysms are heart failure hemorrhage from the aneurysm or cerebral hemorrhage Pathogenesis of the cardiac failure is unknown but may be related to the narrowing of the aortic lumen by compression from the dissection

Antemortem diagnosis of dissecting aneurysm is being made with increasing frequency History and physical exam ination may be of limited value because of the patient s con dition Excruciating epigastric or precordial pain with atypi cal radiation strongly suggests dissection Clinical shock is usually present though hypertension is sustained Pares thesias and altered peripheral circulation may be noted There is no specific ECG pattern Lack of specific changes of myocardial infarction tends to support the diagnosis of dis section in equivocal cases X ray examination of the thorax is the most useful diagnostic aid The aortic wall is normally 2 3 mm thick and widening over 1 cm is diagnostic of an intramural aortic hematoma Without intimal calcification it is impossible to measure the thickness of the aortic wall and diagnosis is more difficult

Recent progress in cardiovascular surgery makes early diagnosis of this condition mandatory Attempts to open the dissecting lumen into the aortic lumen surgically have been successful in 2 of 6 patients in which it has been attempted Re entry permits restoration of peripheral circulation and removes the increasing tension on the outer wall which otherwise predisposes to rupture Two factors are impor tant control of hypertension during and after surgery and early intervention in acute cases

Splenorenal Arterial Anastomoses are reported by Elliott S Hurwitt Bernard Seidenberg Henry Haimovici and Don ald S Abelson[8] (Montefiore Hosp New York) Splenorenal

(8) C culat on 14 532 539 Oct be 1956

tation somewhere within the abdominal aorta A systolic bruit over the lumbar area was heard in several cases and may be helpful

Symptoms resembling intermittent claudication were reported by 5 patients None had symptoms in the buttocks or thighs Angiography particularly translumbar aortography is the diagnostic method of choice The most important factor in operability is proximity to renal arteries

Woman 32 had severe hypertension for several years first discovered during pregnancy Each of 5 pregnancies terminated in spontaneous abortions thought to be due to eclampsia Intermittent claudication in both legs had been present for 6 years and bilateral lumbar sympathectomy had given no relief She had trophic changes in the toes and gangrene in one toe In the 4th month of her fifth pregnancy she had sudden nausea vomiting severe occipital headache and blurred vision and collapsed

On examination she was unresponsive Eye movements were uncoordinated and nuchal rigidity was present. There were hemorrhages exudates and papilledema in the retinal fundi Blood pressure was 210/110 mm Hg in the upper extremities and 100 systolic in the lower extremities The pulse rate was weak in the femoral and popliteal arteries and not palpable below The heart was enlarged and a loud systolic murmur was present A systolic bruit was audible about the umbilicus and also present over the 11th thoracic vertebra

The cerebrospinal fluid was bloody She had albuminuria and occasional leukocytes erythrocytes and granular casts in urine The white blood count was 19 450 and hematocrit 45% Nonprotein nitrogen was 49 mg /100 ml The uterus was evacuated of a twin pregnancy in the hope of avoiding a fatal outcome On the 9th postoperative day she suddenly complained of severe crushing substernal pain became cold cyanotic and unresponsive and died

At autopsy the aorta was found to be sharply constricted just below the origin of the renal arteries A friable thrombus extended upward from the narrowed point occluded the orifice of the left renal artery and impinged on but did not occlude the right renal orifice. The brain contained an old subarachnoid hemorrhage and the lungs were congested The heart weighed only 355 Gm and the left ventricular wall was 1 5 cm thick

Chronic (Healed) Dissecting Aneurysms Dissection of the aorta is usually characterized by the sudden onset of tearing pain frequently radiating followed by loss of consciousness prostration shock coma and death This is the acute variety A few of these aneurysms show evidence of attempts at healing and 5 such cases are reviewed by John T Prior Robert T Buran and Theodore Perl[7] (State Univ of New York Syracuse)

(7) J Thorac S rg 33 213 228 F bruary 1957

In this hospital angiography is performed by percutaneous technics using local anesthesia and basal narcosis Simple percutaneous needle puncture is used when possible For the intrathoracic aorta and great vessels or upper abdominal aorta percutaneous arterial catheterization is used The carotid artery is used for intrathoracic lesions simple needle puncture of the lumbar aorta or femoral artery or percutaneous catheterization of the aorta or iliac arteries from the femoral artery is used for visualization of the abdominal aorta and its main branches

Intrathoracic lesions investigated included coarctation of the aorta intrathoracic thrombosis of one of the common carotid arteries thrombosis of the internal carotid intra thoracic thrombosis of the subclavian and stenosis localized stenosis of the internal carotid and aneurysms of the aorta Lesions encountered below the diaphragm included congenital anomalies of renal and iliac arteries coarctation of the abdominal aorta thromboses of the iliac femoral and more distal arteries aneurysms of the abdominal aorta and arteriovenous fistulas

Direct surgical operations are justified in only a minority of patients with obliterative vascular disease Treatment of choice for the majority is conservative with long term anti coagulants Surgical treatment of aneurysms is justified if they threaten life or cause severe symptoms Repair may be by direct anastomosis thromboendarterectomy autogenous or homologous blood vessel graft or implant of plastic material Other procedures are rarely used

Arterial banks are rapidly becoming obsolete Plastic prostheses are preferred for arteries the size of the external iliac or larger For peripheral arteries the homologous arterial transplant is still preferred although an autogenous vein graft may give better results and plastic prostheses may soon become available

Arlidin Clinical Evaluation of a Peripheral Vasodilator with Selective Action on Muscle Vessels Many drugs and procedures have been tried for therapy of peripheral vascular disease but have proved ineffective Intra arterial epinephrine induces marked dilatation of vessels in muscle and vasoconstriction of vessels of the skin but this type of therapy is impractical Arlidin (1 [p hydroxyphenyl] 2 [1

arterial anastomoses may be lifesaving or result in renal salvage under a variety of circumstances including aortic thrombosis or aneurysm renal artery obstruction injury or aneurysm and anomalous renal artery Experiments in dogs demonstrated that the splenic artery can deliver to a kidney an amount of blood adequate to sustain normal existence

Man 44 with the Leriche syndrome consisting of claudication, loss of sexual potency and absence of pulsations in the lower extremities had complete obstruction of the aorta just below the origin of the inferior mesenteric artery demonstrated by aortography The obliterated segment was resected and replaced with a preserved aortic bifurcation homograft An aortogram 88 days later revealed complete thrombosis of the terminal aorta and graft with the occlusion extending proximally to the level of origin of the renal arteries and slightly higher on the right side A left splenorenal arterial anastomosis was constructed to prevent the anuria that would result should the aortic thrombosis ascend

With a combined thoracoabdominal approach the spleen was mobilized and removed and the splenic artery amputated at the hilus of the spleen and temporarily clamped The left renal artery was mobilized close to its origin from the aorta It was pulsating vigorously although the aorta below it was not. Both the splenic and renal arteries were 3/16 in in diameter The renal artery was ligated practically flush with the aorta End to end anastomosis was effected between the proximal limb of the splenic artery and the distal limb of the left renal artery with doubly armed sutures of 5 0 silk The arteries were clamped with bulldog clamps for 30 minutes during the anastomosis After release of the clamps good pulsations were felt in the main branches of the left renal artery Although there were major postoperative problems the left kidney functioned normally Both kidneys were functioning well as indicated by intravenous pyelogram and urine and blood urea nitrogen level were normal 15 months postoperatively

Discussion on Clinical and Radiologic Aspects of Diseases of Major Arteries is presented by H H G Eastcott David Sutton and C G Rob[9] (St Mary s Hosp London) Arteriography has been helpful in planning treatment for arterial disease and has provided information about earlier changes in vessels Gangrene of the foot is common and usually due to atheromatous disease and spreading thrombosis of the main arterial supply readily shown by arteriograms However some patients have gangrene due to arteriolar disease affecting the smaller vessels vascular spasm and massive thromboses of the whole venous system In these the arteriogram reveals normally patent large vessels

(9) Proc Roy Soc Med 49 557 57 1956

could not be produced by severe exercise and in 7 exercise tolerance was increased but severe effort induced mild claudication One patient received no benefit and in 3 who had early dry gangrene the limb deteriorated after the implant and high amputation was required

Pre and postoperative studies showed increase in circulatory efficiency after treatment evidenced by increased walking distance exercise tolerance by ergometry loss of rest pain and normal radioactive sodium metabolism In 20 control patients who received macerated amnion neither subjective nor objective improvement occurred The main difference between the two types of amnion was the presence of an effective well defined nucleated epithelial and stromal layer

The implants were absorbed in about 3 weeks and gave rise locally to vigorous outgrowth of capillaries Clinical improvement began in about 3 days and was maintained for an indefinite period as yet undetermined Two cases maintained improvement for over 3½ years 7 for over 1 year and the rest over 8 months If one implant is ineffective reimplantation must always be carried out until claudication disappears

► [The results are rather surprising because the rationale for the procedure is not clear at present This method of treatment should be confirmed by other investigators before being widely adopted —Ed]

Measurement of Capillary Pressure in Rectal Mucosa as an Index of Portal Vein Pressure Recognition of portal hypertension was formerly limited to clinical observations such as collateral vascularization meteorism and ascites Later developments have made possible early recognition of portal stasis and its differentiation from portal hypertension Both often but not necessarily occur together While in measurement of circulation nonbleeding methods prevail there has been no method for measurement of portal pressure without puncture of the portal vein esophagus hemorrhoidal veins superficial abdominal varices persistent umbilical vein or spleen Hence L Demling F Wachsmann and F Wolf[3] (Univ of Erlangen) sought a measureable entity directly related to portal pressure that would not require vascular puncture

In considering reliability approximate measurement of pressure in capillaries and postcapillary venous plexus is sat

(3) Deutsch med W h sch 81 1153 1156 J ly 20 1956.

methyl 3 phenylpropyl amino] propanol hydrochloride) is related to epinephrine is effective orally and has its chief peripheral effect on the vascular bed of exercising skeletal muscle Irwin D Stein[1] (Mount Vernon N Y) evaluated this therapy in 220 patients with intermittent claudication

In 21 patients intermittent claudication began acutely but it developed slowly and gradually in 199 In the latter group Priscoline® Ilidar® Roniacol® papaverine Dibenzylene® Hydergine and other commonly used vasodilators had little effect in increasing walking tolerance except for the initial salutary effect seen in the initial use of most new drugs In contrast on oral Arlidin 6 or 12 mg 3 times daily two thirds of these patients had significantly increased ability to walk Intra arterial injection of one 6 mg dose increased blood flow in the calf an average of 300-400%

There was no increase in skin temperature or oscillometric readings no reopening of closed blood vessels with reappearance of pulsations and no improvement in reactive hyperemia Intermittent claudication is characteristic and unmistakable and under standard conditions the amount of muscular exercise needed to induce it is constant *Improvement can be accurately measured by the increase in* exercise tolerance Arlidin is an effective dilator of blood vessels in skeletal muscle and should be used in management of intermittent claudication

Amnion Implantation in Peripheral Vascular Disease was done in 40 cases by E Troensegaard Hansen[2] (Charing Cross Hosp London) Intermittent claudication was due to arteriosclerosis in 38 patients and to Buerger s disease in 2 Symptoms had been present for more than 6 months in most and had not responded to conservative therapy Three patients had sympathectomy without effect on the claudication

Human amnion was collected immediately after delivery and stored at 0 C for 5 days It was then cleaned on the chorionic side only without damaging the epithelial layer After it boiled for 3 minutes it was ready for immediate use and was implanted under local anesthesia in 2 pieces 7×5 cm tightly rolled together deep in the fat lying on the fascia lata on the lateral aspect of the thigh

In 29 of the 40 patients claudication disappeared and

(1) Ann. I t. Med 45 185 190 A gust, 1956
(2) Brit. M J 2 262 268 Aug 4 1956

while rectal anematizing pressure was 100 mm In patients with hepatitis anematizing pressure averaged 200 mm H O (170 280 mm) in those with cirrhosis 300 mm H O and over (300 400 mm) In some individual patients with cir rhosis considerably lower pressures were found perhaps be cause of increased portal circulation through collateral vessels

Splenoportal Venography for Evaluating Abnormalities of Portal Circulation A K Basu and A Das[4] (Calcutta) made 46 percutaneous splenograms Most of the patients subsequently underwent splenectomy splenorenal shunt or ligation of hepatic and splenic arteries

In 12 cases the splenic and portal veins were dilated and tortuous and no collaterals were present Bifurcation of the portal vein at the porta hepatis was seen intrahepatic radi cles were faint and peripheral branches indistinct This was the pattern of tropical splenomegaly of uncertain origin and at surgery no cirrhosis was found

Infrahepatic obstruction was present in 6 cases in which the dye terminated abruptly at some point In cavernoma tous transformation of the portal vein the dye became dif fusely distributed over numerous small tortuous channels In both types many collaterals were present In 23 cases of intrahepatic obstruction due to cirrhosis of the liver distor tion poor visualization irregular branching of intrahepatic radicles pooling of dye and numerous collaterals were prom inent The left gastric and paraesophageal series were most commonly seen as collaterals In secondary portal cirrhosis following long standing splenomegaly the main splenic and portal veins were dilated and tortuous In suprahepatic obstruction the intrahepatic radicles of the portal vein were prominent and well visualized to the periphery without dis tortion of intrahepatic channels or evidence of dye pooling

Portal hypertension can be assessed with fair accuracy from venographic patterns The presence of collaterals is the most significant indication and more accurate than clinical indications such as recurrent hematemeses prominent ab dominal venous collaterals ascites or esophageal varices Portal venography can also assess liver cirrhosis by the pres ence and extent of collaterals Infrahepatic obstruction can

(4) B t M J 2 916 919 O t 0 1956

isfactory because this has a steady relationship to pressure in efferent vessels In the portal region measuring pressure in a capillary area belonging to the portal circulation permits an estimate of pressure in the portal vein Such a region can be reached in the upper rectum by means of the proctoscope Venous outflow from this region is principally by way of the superior hemorrhoidal veins into the portal vein Crescent like folds varying in number allow bilateral compression Largest of these is about 8 cm from the anus Muscular base of the plicae forms the sphincter ani tertius The plica terminalis usually lies principally oralward at the edge of the sigmoid In practice the highest possible fold is chosen for application of pressure Criterion of anematization is first spotty pallor of compromised mucosal area easily recognized with the naked eye Measurements are always performed by the same trained observer

With the original apparatus devised by the authors for measurement of rectal capillary pressure a controlled measurable pressure could be exerted on the transverse plicae but not without production of considerable friction This disturbing factor required repeated standardization of the instrument To avoid this inconvenience two new instruments were developed which function according to the same principle In both measurement of pressure necessary to produce anemia is carried out without transmission through a long conduction rod (which results in too much friction) The first measures anematization pressure purely mechanically The second utilizes the principle of the spring balance with pressure registered electrically Friction is thus reduced to a minimum

Practical use of this method was tested in 170 determinations 110 were made with the original instrument With this anematization pressure in the normal averaged around 130 mm H O in hepatitic patients 190 mm H_2O and in patients with cirrhosis up to 260 mm H O According to later observations with the improved models friction evidently led to some lowering of the values Later studies were made principally with the mechanical instrument (Model I) in 60 subjects Normal value (27 subjects) averaged 90 mm H O (60-120 mm) In 1 case pressure in liver capillaries measured with a catheter was 78 mm H O

The most striking results have been decreased incidence of bleeding and dramatic clinical improvement in many patients after surgery Such improvement had not occurred before operation even after prolonged adequate medical treatment Changes included a feeling of well being and strength improved appearance normal skin color weight gain regrowth of sparse axillary and pubic hair and in some patients disappearance of ascites and edema

► [After some years of debate and uncertainty it would appear that the beneficial effect of venous shunt surgery is now well established in patients with hemorrhage from esophageal varices as the result of portal hypertension —Ed]

THE KIDNEY

Recent Advances in Management of Renal Disease in Children —*Part I*—Current therapy is reviewed by Wallace W McCrory and Duncan Macaulay[6] (Univ of Pennsylvania) Acute glomerulonephritis in children has a low immediate mortality and a low incidence of progression to a chronic state Second attacks were rare even when further streptococcic infections supervene Since it is a self limiting disease with a good prognosis it is difficult to assess the effect of new remedies Many cases would be required to demonstrate significant improvement and few physicians are apt to see enough patients to justify such a demonstration In day to day management of the disease symptomatic treatment is often of benefit to the patient and an attitude of therapeutic nihilism is unjustified Antihistamines are of doubtful benefit and adrenal steroid therapy has proved unsuccessful

Chemotherapy will not influence existing renal lesions but penicillin usually eradicates the streptococci from the upper air passages If there is an infection elsewhere cultures should be taken and chemotherapy determined by sensitivity tests Most children dying in the acute stage have serious infections along with nephritis Apart from infections hypertensive encephalopathy cardiac failure and acute renal failure make the acute phase perilous The incidence of hypertension is 50% and signs of encephalopathy are indications for the use of hypotensive drugs A combination of

(6) P di t 19 481 498 M r h 1957

be diagnosed with certainty by portal venography alone the site localized and often its nature indicated Venography can help plan suitable surgery in abnormal portal circulation

Effect of Venous Shunt Surgery on Liver Function in Patients with Portal Hypertension *Follow up Study of 125* **Patients Operated on** *in Last 10 Years is presented by* Daniel S Ellis Robert R Linton and Chester M Jones[5] (Harvard Med School) All survivors living at the time of the report were followed for at least 1 year and the longest follow up was 10 years Esophageal varices were demonstrated by x ray preoperatively in each patient and hemorrhage was the indication for shunt surgery

Splenectomy and splenorenal anastomosis were done in 88 patients of whom 21 eventually died a mortality of 24% Direct portacaval anastomosis was done in 37 with a mortality finally of 40 5% The over all mortality was 29% with an operative mortality of 11% In patients with alcoholic cirrhosis total mortality was 50% 32% in the postnecrotic group and 16% in patients with normal livers and extra hepatic block Of the 23 late deaths only 12 were due to liver failure and 2 to further esophageal bleeding

Of those who survived operation only 9 died in the first 12 months This is a significant increase in survival in the first year compared with the previously reported survival of only 30% of patients who had esophageal bleeding and did not have surgery

Some bleeding occurred postoperatively in 18 patients (15%) Postoperative x ray examination of the esophagus in 76 patients correlated well with decreased occurrence of bleeding The size of varices was markedly reduced in 81% of patients with splenorenal shunts and in 37% no varices could be demonstrated Comparable results were obtained in 84% and 47% of patients who had portacaval shunts

Liver function tests before and after shunt surgery showed serum albumin to be improved in 29% the same in 53% and worse in 18% cephalin flocculation improved in 40% was the same in 40% and worse in 20% serum bilirubin improved in 30% was the same in 50% and worse in 20% and bromsulfalein retention was improved in 23% the same in 31% and worse in 46%

(5) New England J Med 54 931 936 M y 17 19 6

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(6) Ped tn 19 481-498 M ch 1957

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(5) N w E gland J M d 254 931 936 May 17 1956

Diuresis may be induced by concentrated human serum albumin or hypertonic dextran but daily injections are required Salt restriction lessens the edema accumulation but may lead to salt depletion Mercurial diuretics should not be used Exchange resins acetazolamide (Diamox®) watermelon extract urea and thyroxin have no place in the treatment of renal disease

Adrenal steroid hormones are of definite value in the treatment of edema in children with the nephrotic syndrome Maximal symptomatic benefit depends on prolonged or maintenance therapy Treatment is begun in all patients as soon as the diagnosis is made even though edema may be minimal Hypertension elevated nonprotein nitrogen and/or hematuria are not necessarily contraindications but do increase the likelihood of serious untoward reactions The type of steroid used makes little difference as long as dosage is adequate Diuresis usually occurs after 1 2 weeks of therapy If it has not occurred in 28 days further continuous therapy is of little value Long term maintenance with steroid therapy has reduced the requirements for hospitalization and children apparently live longer and do better than on any previous management

Pyelonephritis in infants and children has the same potentiality for chronicity and serious complications as in adults Therapy usually is not successful The most important cause of failure is the presence of an abnormality of the urinary tract Another is emergence of organisms resistant to commonly used antibiotics Catheterization and instrumentation carry a definite risk The longer an infection has persisted the less likelihood there is of rapid cure In the usual case with acute onset and without constitutional upset sulfonamides are probably sufficient If severe enough to require hospitalization therapy should be determined by urine cultures and sensitivity tests

Renal glycosuria produces no symptoms is usually discovered accidentally and has no known adverse effect on health Carbohydrate intake should not be restricted and insulin is contraindicated

Nephrogenic diabetes insipidus is a congenital defect in which the renal tubules are insensitive to posterior pituitary hormone The clinical picture is that of diabetes insipidus resistant to vasopressin A large water intake and a small

reserpine and hydralazine hydrochloride is the treatment of choice The etiology of cardiac failure in acute glomerulonephritis is unknown but this complication should be treated with oxygen digitalis sedatives hypotensive drugs if necessary salt restriction and in severe cases with pulmonary edema by phlebotomy

Bed rest is obligatory in the early stages but usually not beyond the first month In the second month activity is increased gradually and the child is allowed to return to school Ordinarily limiting protein intake is of little or no value If there is edema or hypertension salt should be restricted Usually it is enough to omit salt in cooking and at the table In more severe cases sodium free bread and milk can be used After diuresis these children have no difficulty in dealing with salt loads

If a case of nephritis appears in a community it may be assumed that nephritogenic strains of streptococci are prevalent and all streptococcic infections whether of the respiratory tract or the skin should be treated with penicillin immediately

Renal lesions of anaphylactoid purpura are frequent and of graver significance than acute glomerulonephritis Pathologically the lesions are those of subacute glomerulonephritis Adrenal steroid therapy has no favorable effect The management is that of any unhealed nephritis i e avoidance of infection and vigorous treatment of any intercurrent infection

The nephrotic syndrome (proteinuria hypoproteinemia edema and hyperlipemia) is commonest in children aged 1 3 with no evidence of other systemic disease and no history of preceding acute glomerulonephritis The primary injury is probably to the glomerulus permitting loss of serum proteins into the urine The course in children is unpredictable It may be one of recurrent relapses and remissions or fulminating Death due to renal failure occurs in about 50% of patients Treatment is symptomatic Susceptibility to infections is increased Antibiotics in therapeutic dosages to eradicate infections and as a prophylaxis to lessen their frequency has been a major advance in management In general physical activity is not a factor in the course of the disease and need not be restricted In the diet a high protein intake is desirable

accompany alkalosis which may be corrected by calcium

Hyperphosphatemia is usually associated with hypocalcemia but this rarely causes tetany Restricting the milk intake and supplementing with calcium will usually relieve the hyperphosphatemia Aluminum hydroxide gels have helped Patients with this condition appear to feel and act better if protein is restricted Adequate calories and vitamins are essential Prolonged feedings low in protein may deplete the potassium stores and supplemental potassium may be necessary This requires close surveillance Blood transfusions may be beneficial to patients with significant anemia Complications such as salt depletion or increase in azotemia may be precipitated by infection dehydration and gastroenteritis These should be searched for and corrected

Acute renal failure manifested by oliguria or rarely anuria is usually due to circulatory collapse transfusion reaction toxins or accidental poisoning The course after acute tubular damage may be short or prolonged and clinical manifestations mild or severe Existing disturbances which caused the acute renal failure should be corrected promptly if possible

Pulmonary edema and cardiac failure can usually be prevented if excessive fluid is avoided during the period of oliguria If the condition is not due to inadequate fluid intake fluid intake should be normal for the first 24 hours and thereafter restricted to 750 ml /sq m of surface area plus the volume of urine excreted Weighing the patient daily and recording the fluid intake and output are essential Dietary protein should be eliminated during the oliguria Marked derangement in acid base balance should be corrected During diuresis frequent determinations of electrolyte concentrations are important

The cause of death in uremia is still obscure Hyperkalemia is the only clearly recognized electrolyte disturbance capable of causing death Fruit juices and other sources of potassium must be restricted Dextrose infusions insulin and calcium may reduce the hyperkalemia but the effect is usually transient Exchange transfusions have been used but hemodialysis if available seems the most effective treatment

Lavage of some segment of the bowel and intermittent

renal solute load are especially recommended in such cases

Patients with renal tubular acidosis excrete an alkaline, neutral or weakly acid urine in the presence of a systemic acidosis Chloride concentration is increased in the serum rather than in undetermined fixed anion The localization and nature of the primary tubular defect are unknown but the kidney does not conserve fixed cations resulting in abnormal losses of bicarbonate as sodium potassium and calcium salts Secondary hyperparathyroidism may develop in an attempt to maintain a normal calcium concentration in the plasma Therapy is aimed at replacing the alkali as the sodium salt of citrate lactate or bicarbonate Sodium chloride is useless or even harmful

In the Fanconi syndrome many tubular defects are found simultaneously Therapy is directed at treating the rickets with large doses of vitamin D correcting the acidosis if possible with alkalis administering potassium and ensuring adequate fluid intake

Renal osteodystrophy may be suspected if symptoms of bone pain develop X rays usually show rickets and demineralization may be found Correcting the acidosis and administering vitamin D are often dramatically successful Healing may be faster if the calcium intake is high

Part II—McCrory and Macaulay[7] state that chronic renal insufficiency may be recognized by typical symptoms of retarded growth recurrent vomiting dehydration without *apparent cause convulsions refractory anemia and* bone disease Early recognition is important since the rate of renal function deterioration can be lessened by eradicating associated active infection of the urinary tract

Exact diagnosis is essential to appropriate therapy Increased fluid intake is necessary to permit excretion of solutes by a kidney with limited concentrating and diluting abilities Excesses or inadequacies in intake are not tolerated Body electrolytes should be maintained to keep the patient feeling at his best rather than chemically normal Hyponatremia is easily induced if sodium is not provided. Sodium and potassium wasting are rare but may develop Some *degree of acidosis is tolerated but if marked* must be corrected with sodium lactate or bicarbonate Tetany may

(7) Pediat cs 19 639 650 April 1957

concentrated and acidic If the urine is alkaline a few crystals of sodium chloride or some concentrated hydrochloric acid may prevent dissolution of the casts

Casts are often found in urine properly examined from office and hospital patients Identification can be valuable as a screening test and in the discovery of masked or asymptomatic renal disease The casts are of specific diagnostic value permit correlations with renal physiology and pathology and are helpful in treatment and prognosis The examination should be done by the physician

Hyaline casts are the gel of proteins which have presumably traversed the capillary membrane Their formation depends on concentration of protein and other solutes and on acidification Formed elements present at the time of gel formation are entrapped and are an indication of the condition in the nephron When a significant number of hyaline casts are broad loss of nephrons or obstruction with subsequent dilatation is inferred The casts may be seen in small numbers in apparently normal urine and increase with exercise

Red cells in a cast mean renal hematuria they should always be considered pathologic They may be the only manifestations of acute glomerulonephritis subacute bacterial endocarditis renal infarction or collagen kidney When they increase the cast appears orange yellow Addis considered the blood cast which is homogeneous without distinguishable cell margins pathognomonic of acute glomerulitis

Leukocytes in casts are renal in origin They may be seen in acute glomerulonephritis and nephrotic syndrome but more often signal infection Bacteria in casts are pathognomonic of renal infection and are easily seen with phase contrast microscopy or glitter cell stain Granular inclusions *may* arise *from degenerated cells* bacteria or unknown flotsam and jetsam in the nephron stream Doubly refractile fat bodies (cholesterol esters) may be found free in casts especially in intercapillary glomerulosclerosis with proteinuria Fatty inclusions are found in the nephrotic syndrome Kimmelstiel Wilson disease scleroderma kidney lupus periarteritis miliary infarction and the recovery phase of acute renal insufficiency with tubular necrosis Fat bodies are more numerous in the presence of hyperlipemia

Epithelial casts are fused from desquamated tubular cells

peritoneal lavage have been described Renal decapsulation appears futile and is hazardous

Relationship between Renal Function and Clinical Course in Chronic Renal Failure Based on 29 Autopsied Cases Poul Effersøe[8] (Copenhagen) selected only patients whose kidneys at autopsy were less than half the normal size or who had established congenital cystic kidneys

From 3½ years to 6 months before death the serum creatinine concentration was fairly constant in the individual patient but varied from one patient to another Six months or more before death the concentration was less than 11 mg/100 ml in each patient studied In the next 3 months it rose above 15 mg/100 ml in about half the patients and during the last 3 months no further appreciable rise occurred except in a few patients during the terminal 2 weeks

In patients with at least 5% of renal function during the last 3 months of their illness serum creatinine concentration was high only if there were severe cardiovascular damage or purulent urine In the group whose renal function had fallen below 5% during the last 3 months of life only one third had such complications This group represents the patients with chronic renal disease who die from pure excretory failure Characteristically these patients can live several years if renal function is above 5% of normal (serum creatinine below 11 mg) When renal function falls below 5% (serum creatinine above 11 mg) death will occur in 3-6 months

Although the number of patients in each subgroup is small no significant difference was noted between those who had glomerulonephritis pyelonephritis or cystic kidneys The studies do not confirm the impression of some clinicians that patients who have chronic pyelonephritis or cystic kidneys live longer than patients who have chronic glomerulonephritis with the same degree of renal impairment On the contrary the prognosis seems independent of the type of renal disease once renal function has fallen below 5%

Identification and Clinical Significance of Casts are discussed by George E Schreiner[9] (Georgetown Univ) A fresh clean voided specimen should be examined preferably

(8) Acta med sc d v 156 435-448 1957
(9) A M A A ch I t M d 99 356 369 M ch 1957

tion and continued delineation of the natural history of glomerulonephritis are most important

Exacerbation of chronic glomerulonephritis is often difficult to differentiate from acute glomerulonephritis Meticulous perusal of previous medical insurance employment selective service and military records is helpful as is a history of antecedent edema periorbital swelling chronic retinal changes or the finding early in the present course of hypoproteinemia and albuminuria of significant proportions or of the nephrotic syndrome The latent period between infection and signs of clinical nephritis is much shorter in exacerbation and increase in antistreptolysin titer is more likely to follow than precede the clinical signs

Recurrent sore throat persistent cervical lymphadenopathy low grade fever headache nausea and vomiting lethargy anorexia and circles or puffiness under the eyes may mean delayed convalescence recurrence of the original infection or onset of clinical acute glomerulonephritis Fresh urinary sediments must be examined frequently sedimentation rate determined and serum complement measured Finding typical blood casts is most helpful

Proteinuria occurs in many infectious diseases and has been explained on the basis of increased permeability of glomerular capillaries acute glomerulitis or focal glomerulonephritis There is no latent period between onset of infection and onset of urinary findings and the infection need not be streptococcic Urinary sediment findings are sparse

Posture sensitive proteinuria is reported in 2 30% of young people The diagnosis is probable when the horizontal urine is normal the vertical abnormal and a full renal evaluation negative The quantity of protein is usually less than 1 Gm /day Without biopsy the absence of latent glomerulonephritis cannot be proved

Focal necrotizing glomerulonephritis as that in subacute bacterial endocarditis can present most of the signs and all the urinary findings of acute glomerulonephritis Hypertension and edema however are rare and uremia uncommon Positive blood cultures anemia heart murmurs splenomegaly embolization and bacteriuria may be helpful for differentiation Focal suppurative glomerulonephritis is produced by direct action of bacteria on glomerular capillaries is a

which form in rows of two or three An occasional renal epithelial cell or clump is not remarkable but many may indicate wholesale desquamation and sloughing Degeneration of the discrete cellular cast into coarsely and finely granular material is a function of age and implies stasis in the nephron. Waxy casts represent the homogeneous degeneration of cells into a highly refractile yellow cast seen frequently in chronic diseases with scar tissue and tubular dilatation The most significant cellular cast is the broad renal failure cast which is usually yellow and slightly granular and appears with increasing incidence in renal failure

In addition to interpretation of individual casts information may be obtained from the other elements in the urine Red cell casts in a urine with a high percentage of broad casts suggest acute exacerbation of chronic glomerulonephritis or recent infarction of renal tissue The so called telescoped urine sediment may be seen in the kidney of subacute bacterial endocarditis in collagen kidney in various states and with a combination of stages of glomerulonephritis The components of this telescoped sediment are manifestation of acute glomerulonephritis (red cells hyaline casts with red cell inclusions blood casts and positive benzidine) the nephrotic syndrome (massive albuminuria hyaline casts cellular casts oval fat bodies and doubly refractile fat bodies) and chronic glomerulonephritis (less albuminuria pigmented granular casts waxy casts and broad and renal failure casts)

► [Patients with inflammatory disorders of the lower urinary tract may have small amounts of albumin in the urine However they do not display casts which are formed only in the kidney Therefore the finding of casts constitutes conclusive evidence that the albumin or at least some of it is of renal origin If the urine is examined immediately after being voided, casts will be found in practically every instance of proteinuria of renal origin unless the urine is alkaline —Ed]

Differential Diagnosis of Acute and Chronic Glomerulonephritis includes a wide variety of organic renal and vascular diseases and some functional causes of proteinuria Diagnostic accuracy and therapy can be improved by proper integration with the laboratory improved examination of the urinary sediment better bacteriologic studies and serologic technics more frequent testing of discrete renal functions and the recently introduced renal biopsy According to George E Schreiner[1] (Georgetown Univ) keen observa

(1) J Ch o D 5 45 66 J ary 1957

is increased circulation time is prolonged or ventricular gallop rhythm is present before hypertension or nephritic urinary findings are noted Other glomerular diseases which should be considered are fulminating forms of intercapillary glomerulosclerosis (Kimmelstiel Wilson disease) amyloid disease and uric acid nephritis

When a patient has a clear history of acute glomerulonephritis a documented nephrotic syndrome or proteinuria of long standing and examination shows edema hypertension uremia progressive renal failure proteinuria hematuria or cylindruria the diagnosis of chronic glomerulonephritis will usually be reached Without a clear history differential diagnosis must include almost all the organic renal diseases including chronic pyelonephritis primary vascular disease polycystic disease intercapillary glomerulosclerosis renal amyloidosis renal lesions of systemic lupus erythematosus scleroderma nephrocalcinosis and uric acid nephritis Adequate history physical examination and laboratory findings may differentiate these entities but occasionally diagnosis may depend on renal biopsy

Resolution of Nephrotic Syndrome The nephrotic syndrome is characterized by edema proteinuria hypoproteinemia and hyperlipemia In addition hematuria hypertension or nitrogen retention may be present Spontaneous or induced resolution of edema may occur but disappearance of proteinuria the only criterion of complete recovery is rare L Eales (Univ of Cape Town) observed 56 consecutive patients with the nephrotic syndrome (seen before the introduction of therapy) and 39 additional patients treated with steroids Only 3 probable recoveries were encountered in each group

Reported recoveries in the literature must be accepted with reservations unless sufficiently long and careful observations are also recorded Recovery in the adult is rare Prospects of recovery appear to be better in children with cases conforming to the diagnosis of so called lipoid nephrosis but here also prolonged observations may reveal evidence of activity years later Differences in the underlying causes may be the major factors in the differences in prognosis Hitherto unrecognized disease states may be present as the nephrotic

(2) S th Af J Lab & Cl n. M d 2 179 205 S pt mb 1956

manifestation of infection and is closely related to or indistinguishable from miliary abscesses or hematogenous pyelonephritis It occurs at the peak of the associated disease with no latent period Urinary findings tend to increase or decrease with fever and degree of sepsis

Acute pyelonephritis may be difficult to distinguish from acute glomerulonephritis characterized by septic course fever chills and headache Uncomplicated acute pyelonephritis can usually be differentiated by the persistently febrile course and characteristic urinary findings of bacteriuria and pyuria with or without clumps of leukocytes and glitter cells observed under reduced light with an ordinary microscope Gram stained smears and quantitative colony counts on urine cultures help separate these two diseases Periorbital edema is uncommon and the nephrotic syndrome is virtually absent Pyelonephritis is a common cause of microscopic and even gross hematuria It may lead to necrotizing papillitis anuria or oliguria and may furnish sloughed renal epithelial cells and doubly refractile fat bodies

The nephrotic syndrome is a phase of subacute or chronic glomerulonephritis characterized by edema massive proteinuria hyperlipemia and hypoalbuminemia Rarely there may be red cells and red cell casts in the urine and differentiation from acute glomerulonephritis may be difficult

Necrotizing arteritis an accelerated vascular degenerative lesion characterized by intimal thickening fibroblastic proliferation lamination of collagen fibrinoid necrosis intramural hemorrhage and perivascular inflammatory reaction is seen in malignant hypertension periarteritis nodosa systemic lupus erythematosus and sensitivity to antibiotics vaccines and serums It may appear similar to acute glomerulonephritis but age of onset is usually the 4th to 6th decade uncommon years for acute glomerulonephritis A history of antecedent hypertension rapid development of retinopathy and papilledema and lack of associated streptococcic infection are differential points

Acute congestive heart failure may superficially resemble *acute glomerulonephritis most strikingly* in young patients with rheumatic or idiopathic myocarditis Diagnosis of acute congestive failure is favored if the underlying heart disease is identified the heart is enlarged or dilated venous pressure

significantly in 8 patients The rise was usually of increasing measure during the first few days of ACTH administration A precipitous fall in ammonia excretion frequently followed discontinuance of therapy Ammonia ion excretion continued to rise remain elevated or decreased slightly despite sodium diuresis which occurred spontaneously or was initiated by mercurial diuretics

ACTH induced diuresis occurred in 3 patterns spontaneously in the days after ACTH was discontinued as a spontaneous diuresis of sodium and water beginning during the period of administration or as a restored sensitivity to mercurial diuretics after ACTH Patients with nephrosis who responded well to ACTH demonstrated increases of ammonia excretion of 62 to 380% compared with control values before ACTH was administered The mechanism of this rise in ammonium excretion is unknown Probably it is due to a direct effect of ACTH or its hormonal associates from the adrenal cortex on the enzyme system concerned with deamination of glutamine or it may be due to an increased availability of amino acid glutamine

Clinical significance of the rise in ammonia ion excretion is not clear The rise occurred in all 8 patients who responded well to ACTH therapy and did not occur in 2 with failure but the evidence is insufficient to justify its use as an index of good response

Several recent reports have noted unsatisfactory results from ACTH therapy This therapy has proved effective however in this series of patients Rigid control is still demanded of patients by the use of an acid ash salt poor diet with adequate fluid intake adjunctive diuretics when needed and education of the patient before during and after the use of this hormone

Clinical Aspects of Renal Vein Thrombosis In the past most cases of renal vein thrombosis have been first recognized at autopsy but it should now be possible to make the diagnosis clinically C V Harrison M D Milne and R E Steiner[4] (Postgrad Med School London) describe 11 patients in some of whom the condition was recognized or suspected during life and in 4 confirmed radiologically Three cases presented as the nephrotic syndrome and 6 as rapid deterioration of renal function with oliguria One was

(4) Quart. J Med 25 285 298 J ly 1956

syndrome With the advent of effective antibiotic therapy and prevention of death from intercurrent infection a higher recovery rate may be attained

Maintenance of effective osmotic pressure is related to the concentration of serum protein particularly albumin and when reduced fluid is not retained within the vascular system In some patients diuresis is not accompanied by any change in glomerular filtration rate In the nephrotic syndrome cellular metabolism is disturbed and the collagenous ground substance has an increased affinity for water Perhaps diuresis may in part result from alteration in the physical state of this ground substance

On rare occasions remissions may follow infections especially of the lungs peritoneal cavity and the skin The improvement amounts to partial or complete loss of edema but rarely to abolition of proteinuria Measles may in some instances produce diuresis associated with clinical improvement and may produce complete remission of proteinuria usually temporary Malaria may sometimes induce similar results and remissions have been reported after infective hepatitis dengue fever and typhoid and paratyphoid

Evidence for beneficial effects of nitrogen mustard is doubtful Corticosteroids (80 courses of treatment) induced diuresis in approximately 60% of 39 patients The remission was usually short lived and relapse occurred within 1 month of cessation of treatment Proteinuria was permanently abolished in 2 patients both children

Serum albumin has little place in the therapy of the nephrotic syndrome Plasma volume expanders such as dextran may be effective but the hazards of circulatory overloading pulmonary edema severe reactions and further depression of serum protein concentration has led the author to abandon the use of this drug Salt intake was restricted to 2 Gm daily in most patients Mercurial preparations have been the only effective diuretics but they have not been universally effective Diamox® has little effect Abdominal paracentesis and drainage through Southey s tubes are often effective in reducing edema

Effect of Corticotropin (ACTH) on Ammonia Production in Nephrotic Syndrome was studied in 10 patients by G H Heidorn[3] (Great Falls Mont) Ammonia excretion rose

(3) Am J M Sc 231 644-654 J ne 1956

Escherichia coli were recovered in pure growth from 4 of the 6 patients *These 6 had the most difficult urinary tract in fections seen during a 6-month period* In 4 patients the in fection produced a syndrome much more disabling than many chronic urinary infections Two were near death Clinical response to Furadantin® was dramatic and no toxic effects were seen

Man 62 had been treated elsewhere for urinary retention and uremia by an indwelling urethral catheter and antibiotics He had daily temperature elevations with chills and delirium Repeated blood cultures were sterile and various obscure causes for fever were ruled out He had no prostatic abscess or obvious infection in the upper urinary tract Diagnosis was infection in prostate urethra and bladder

Combined treatment with Gantrisin® Terramycin® and streptomycin had no effect A suprapubic cystostomy was performed but fever persisted The organism recovered was Escherichia coli sensitive only to Furadantin® which was started on the 5th hospital day Within 24 hours temperature was normal and remained normal and delirium and chills ended The patient subsequently underwent successful second stage prostatectomy On discharge from the hospital his urine contained Escherichia coli and Pseudomonas aeruginosa both resistant to all antibiotics including Furadantin®

Renal Papillary Necrosis Clinicopathologic Study of 42 Cases The commonest current hypothesis as to pathogenesis is that pyramidal blood vessels are compressed by inflammatory exudate particularly in diabetic persons and by increased intrapelvic pressure caused by obstruction of the urinary tract Of the 42 patients studied by Howard B Simon Warren A Bennett and John L Emmett[6] (Mayo Clinic and Found) 7 had diabe es

Renal papillary necrosis may be divided into subacute and acute types In the subacute type the progression of renal infection is usually slow blood *urea increases oliguria de*velops and finally death occurs This type was found in 12 patients of whom 5 were diabetic When there is obstruction of the urinary tract and complicating cardiovascular disease the clinical picture may in no way suggest the diagnosis of papillary necrosis The acute type has two forms It may be fulminating with fever septicemia rapidly progressing azotemia and oliguria ending in coma or death or it may be due to obstruction of the urinary tract complicated by a terminal acute renal infection rapidly progressing to uremia oliguria and death

(6) J U 1 77 557 567 April, 19 7

a typical example of tumor thrombosis of the renal vein and inferior vena cava and 1 was associated with malignant hypertension

Thrombosis of the inferior vena cava is commonly due to spread from pelvic or leg veins and in most cases is confined to the lower segment of the inferior vena cava The upper end of the clot is usually just below the entrance of the renal veins Extension upward is limited by the considerable increment of blood flow from the kidneys If renal blood flow is temporarily lowered by salt depletion hemorrhage or traumatic shock or permanently reduced by primary renal disease the clot may extend beyond the renal veins Further extension obstructing the hepatic veins is extremely rare

Obstruction of the inferior vena cava by invasion of malignant neoplasms or to external pressure more commonly involves the middle segment because hypernephroma is a frequent cause of tumor thrombosis of the renal veins and vena cava and because of common involvement of retroperitoneal lymph nodes at the celiac axis by metastases

Except during infancy primary renal vein thrombosis is rare probably because blood flow is rapid In adults it may occur as a secondary often terminal complication of renal disease which has previously reduced renal blood flow It may be found in glomerulonephritis and pyelonephritis and is particularly likely in renal amyloidosis

Venography of the inferior vena cava or renal veins is necessary for diagnosis in many cases It may be helpful in patients who have proteinuria with or without edema if any of the following abnormalities are present collateral abdominal veins with upward blood flow unexplained edema of the legs or lower trunk recent pulmonary infarction in which the source of embolus is not obvious evidence of maligant disease or a single kidney

Furadantin® in Resistant Urinary Infections is safe and efficacious A variety of complicated and uncomplicated infections has been treated successfully D W Hofsess[5] (Denver) presents case histories of 6 patients 4 of whom were critically ill from the infection alone each demanding immediate measures for control All patients received 400 mg Furadantin® daily and were treated for 14 days

(5) Rocky Mounta M J 53 902 904 Octobe 1956

saccharides and other proteinaceous substances with the appearance of local basement membrane thickening fibrinoid change hematoxylin bodies and endothelial cell proliferation The kidneys of two thirds of patients ill with systemic lupus erythematosus are involved to a greater or lesser degree by these pathologic abnormalities and their consequences

The course of lupus nephritis may be fulminating with death from renal failure in weeks or it may develop slowly in a patient who has had systemic lupus erythematosus for months or years or may present itself with the gradual onset of a classic nephrotic syndrome which may be the only overt manifestation of systemic lupus erythematosus Usually it progresses inexorably to death in 1 5 years The progress is usually faster than in glomerulonephritis related to streptococcic illness

The earliest lesion of lupus nephritis consists of a local membranous glomerulitis involving small areas at the periphery of the glomerular tuft Small areas of endothelial proliferation are also common These early lesions have been found by renal biopsy in the absence of signs symptoms or laboratory data indicating kidney involvement The urine may be normal or it may contain protein leukocytes in clumps and leukocyte casts—a finding often erroneously interpreted as pyelonephritis Renal function tests are of little help

The glomerular changes and progress of the renal disease may depend on the extent and severity of the initial kidney lesions In the glomerulus progression is indicated by the appearance or increase of fibrinoid material in the basement membrane increase in proliferative lesions adhesions between the tuft and Bowman s capsule and in ome by local areas of necrosis and karyorrhexis

As the renal lesion progresses erythrocytes and granular casts appear in the urine of most patients and epithelial cell casts fatty casts and oval fat bodies in the urine of some Renal function decreases azotemia increases and nocturia polyuria and polydipsia appear If the patients live long enough most will pass through an edematous stage of nephritis associated with hypoalbuminemia hypercholesteremia and much proteinuria When this nephrotic syndrome

The disease is usually fatal although spontaneous healing and recovery have been reported The commonest clinical findings are flank pain chills and fever hematuria dysuria urgency and frequency of urination nausea and vomiting prostration and coma Oliguria develops in all patients at least terminally with associated mounting uremia and coma Death results from uremia or overwhelming infection

The correct diagnosis is rarely made before death If made it is confirmed by x ray examination or by examination of tissue sequestra obtained in the urine The pyelogram is similar to that of renal tuberculosis because of the erosion and destruction of renal papillae The irregular dilatation and moth eaten appearance of the minor calices are pathognomonic resulting from necrosis and sloughing of the renal papillae

No single factor may be cited as all important in the pathogenesis The inferior blood supply of the pyramids localizes the necrotic process to its characteristic site Vascular changes or acute pyelonephritis were seen in each patient and both were present in more than three fourths Obstructive urologic disease and diabetes mellitus either of which may potentiate renal infection and further compromise the pyramidal blood supply were frequent complicating factors

In view of the usual fatal end treatment is largely supportive Control of diabetes and infection and relief of urinary tract obstruction are imperative

The frequent occurrence of renal papillary necrosis in nondiabetics is emphasized

Lupus Nephritis Clinical and Pathologic Study Based on Renal Biopsies in 33 patients with disseminated lupus erythematosus is reported by Robert C Muehrcke Robert M Kark Conrad L Pirani and Victor E Pollak[7] (Univ of Illinois) One third of the patients had normal kidneys or minimal renal change when first studied although they had systemic manifestations of the disease The rest had mild glomerulitis or severe glomerulonephritis

Lupus nephritis is a progressive fatal glomerulonephritis which is the main cause of death in patients with systemic lupus erythematosus In lupus nephritis the glomerular tuft is damaged and reacts to deposits of abnormal mucopoly

(7) Medicine 36 1 145 February 1957

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appears the typical face rash of systemic lupus erythematosus may have disappeared The diagnosis of systemic lupus erythematosus may be overlooked because the better known symptoms and signs of the disease may be absent or minimal when edema develops Usually a carefully taken history established the presence of past symptoms

In this form of the nephrotic syndrome spontaneous or induced diuresis with rapid clearing of water logging is uncommon The edema usually persists for months, and chronic renal failure develops slowly In the edematous phase there may be membranous or membranous and proliferative changes in the glomerular tuft and epithelial crescents may be found Features peculiar to lupus nephritis are usually present Tubular degeneration is evident and fatty changes are demonstrable Interstitial edema and mild fibrosis are common and the vessels may contain fibrinoid Secondary pyelonephritis may be seen clinically and histologically at this stage Progression to chronic glomerulonephritis with contraction of the kidney is rare and hyalinization of the glomeruli is unusual The tubules become atrophic or dilated but severe tubular atrophy is rare Fibrous tissue is laid down in the interstitium and inflammatory cells may appear in large numbers The course is gradually downhill Proteinuria decreases and casts appear in increasing numbers in the urine Renal function becomes abnormal Clinical and laboratory evidence of systemic lupus erythematosus may persist though difficult to demonstrate in some e g the thymol turbidity may return to normal and Hargraves cells may disappear from the circulation At this stage the patient may die of chronic renal failure of an associated infection or during an acute exacerbation of systemic lupus erythematosus with cardiac pulmonary abdominal or neurologic crises Usually death follows chronic renal failure and in many patients the terminal illness cannot be distinguished from any other form of Bright s disease At autopsy the kidney may be indistinguishable from that in late subacute or early chronic glomerulonephritis of the common type Microscopically little or no evidence of the lesions typical of lupus nephritis may be found

In a few cases the disease may be fulminating The glomeruli are severely damaged from the outset Although a

brief history of other symptoms of systemic lupus erythematosus may be elicited onset may be sudden The patient is admitted with much protein in the urine and appears to have the nephrotic syndrome. However serum cholesterol is low This pseudonephrotic picture is usually complicated by other evidence of acute systemic lupus erythematosus such as abdominal crises and myocarditis After a short stormy illness the patient dies in renal failure Histologically glomerular disease is most extensive and active with widespread local necrosis fibrinoid change karyorrhexis hematoxylin bodies and hyaline thrombi Severe tubular damage interstitial edema fibrosis and inflammation are evident

In patients with systemic lupus erythematosus changes in the ground substance of the kidney and its vessels are similar to lesions found elsewhere in the body No etiology other than systemic lupus erythematosus need be invoked to explain lupus nephritis Serial biopsy studies of the kidney provide a sure and simple method to clarify the histogenesis of the renal lesions In the future physical and chemical methods applied to renal biopsy specimens may further elucidate the reactions of the ground substance in this disease

Renal Rickets with Phosphoglucoamino Renal Diabetes (De Toni Debre Fanconi Syndrome) is discussed by G De Toni[8] (Univ of Genoa) with a review of the literature The syndrome is a form of renal rickets with certain biochemical variations i e hypophosphatemia glycosuria and aminoaciduria It occurs principally in children of consanguine parents but cases have been recorded in adults The bony lesions are those of rickets or osteomalacia in the adult and of rickets dwarfism and osteitis fibrosa before puberty Biochemical changes are hypophosphatemia with normal levels of serum calcium hyperchloremia no elevation of blood levels of urea hyperphosphaturia albuminuria hyperaminoaciduria particularly cystinuria normal blood level of amino acids renal glycosuria lowering of blood bicarbonate level usually alkaline urine and an excess of other organic acids in the urine including lactic acid and beta hydroxybutyric acid During the terminal renal insufficiency hyperphosphatemia with low levels of calcium is likely to occur

Some patients have an anatomic abnormality of the uri

(8) A pa d t. 187 42 80 J ly A g 1956

nary tract A number have glomerulonephritis associated with chronic interstitial nephritis and some have been reported who have fairly normal kidneys but intense fatty degeneration of the liver Microdissection has demonstrated anomalies in the shape of the proximal contorted tubules When cystinosis is associated with the syndrome the findings may vary from almost normal kidneys to chronic interstitial nephritis with progressive practically complete destruction of functioning renal parenchyma

The essential features of the syndrome are renal rickets and renal diabetes Glycosuria is essential before the diagnosis can be made The De Toni Debre Fanconi syndrome is not the same disease as cystinosis although the two may coincide Dwarfism seen in children with the former is not always associated with cystinosis

When the condition is associated with cystinosis treatment is discouraging since the tendency is toward progressive deterioration Therapy should be based on alkalinization as in idiopathic renal acidosis it should be directed against the rickets and should include vitamins In practice results have been disappointing since improvement is soon followed by relapse A solution containing citric acid sodium citrate and potassium citrate has been reported as successful and 2 cases have been described in which intramuscular injection of sodium adenosine monophosphate led to resumption of growth

Since improvement does occur and a few patients recover and live to old age despite grave manifestations during infancy the prognosis need not necessarily be gloomy

Renal Tubular Acidosis Five new cases are described by G L Foss C B Perry and F J Y Wood[9] (Southampton England) In this rare clinical syndrome the kidneys cannot produce urine of normal acidity The urine is alkaline or weakly acid with fixed specific gravity and frequently copious in amount Base sodium potassium and calcium are lost from the body in varying proportion resulting in systemic acidosis decreased plasma bicarbonate and increased plasma chloride with a low plasma inorganic phosphate

Renal tubular acidosis has been described in two groups of patients The larger group consists of infants who show de

(9) Q art J Med 25 185 199 Ap l 1956

hydration not due to diarrhea vomiting or inadequate intake of fluids or salts and in whom the disorder is often fatal The second group consists of older children and adults in whom the duration of illness is prolonged and the renal defect is present from birth Treatment with citrates and other alkalinizing salts produces clinical improvement but not cure

Loss of calcium may lead to rickets easily produced fractures deformities and stunted growth Calcium tends to be deposited in kidneys forming stones or nephrocalcinosis Loss of potassium may lead to attacks of muscle weakness varying from mild transient episodes to more severe weakness lasting days and even to extensive and sometimes fatal paralysis of the limbs and trunk Weakness tends to be present when the patient first wakes in the morning but may develop any time of day They may feel tired and apathetic Polyuria and thirst are common Water balance is precarious Vomiting or restriction of fluid for a concentration test may lead to serious dehydration

Treatment is directed toward supplying extra base to enable excretion of acid metabolites in neutral form without depleting the body stores of base This is achieved by giving alkalinizing salts such as sodium citrate potassium citrate and sodium bicarbonate Such treatment has been successful To heal rickets in the shortest possible time massive doses of calciferol and a high calcium diet should be given in addition to sodium citrate If rickets is not gross treatment with alkalinizing salts is adequate and use of calciferol should be avoided since large increase in urinary calcium will further increase nephrocalcinosis

Improvement in physical well being in all 5 treated patients was gratifying The prognosis is unknown Untreated the patient may die of potassium deficiency and progressive renal calcification will lead to extensive renal damage Superimposition of infection and continued calcium deposition can occur even in the treated patient Sulfonamides should never be given to patients with renal tubular acidosis and patients should be emphatically warned not to allow their doctors to give them these drugs

Interpretation of Serum Potassium Concentration Recent reports have emphasized failure of serum potassium to re

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(9) Q t J M d 25 185 199 Ap l 19 6

will reflect the content capacity ratio and therefore the potassium needs of patients

Management of hyperkalemia aims at elevating and maintaining body glycogen stores to increase total potassium capacity and thus decrease serum potassium concentration Reasonable amounts of parenteral glucose should be given continuously

flect intracellular potassium but according to Belding H Scribner and James M Burnell[1] (Univ of Washington) serum potassium properly interpreted is a remarkably accurate guide to potassium requirements

Potassium depletion usually results from gastrointestinal and renal losses of potassium while intake is inadequate An increase in the content capacity ratio usually represents decrease *in total capacity rather than increase in total body potassium* The typical example of potassium excess is acute renal failure where total body potassium remains constant because the kidneys cannot excrete potassium but total potassium capacity decreases as glycogen stores are depleted red cell mass is destroyed and body protoplasm burned

Other factors which decrease total potassium capacity are starvation fever tissue destruction and hemolysis No sustained increase in potassium capacity occurs clinically Acidosis increases and alkalosis decreases serum potassium concentration independently of the ratio total body potassium total capacity However serum potassium concentration properly interpreted reflects the potassium needs of patients In the low range 1 mEq /L changes in serum concentration reflect approximately 3 6% changes in the ratio For example a 70 kg man has a normal total body potassium of 3 500 mEq a fall from 4 to 3 mEq /L in serum concentration represents 100 200 mEq potassium deficit In other words when serum concentration is 3 mEq /L in a 70 kg man he needs at least an additional 100 200 mEq of potassium

Changes in pH can alter the interpretation of serum potassium concentration In severe alkalosis low serum potassium concentration may reflect a normal content capacity ratio The same may apply to high serum potassium in severe acidosis More important in severe acidosis normal serum potassium concentration reflects moderate potassium depletion and low serum potassium reflects profound depletion

Water depletion changes in extracellular space and changes in renal function have no significant effect on this relation Thus in most clinical situations serum potassium concentrations interpreted in the light of extracellular pH

(1) Metabolism 5 468-479 July 1956

The Digestive System

FRANZ J INGELFINGER MD

PART V

THE DIGESTIVE SYSTEM

ALIMENTARY TRACT

Gastroesophageal Sphincter in Healthy Human Beings was studied by F E Fyke Jr C F Code and J F Schlegel[1] (Mayo Clinic and Found) who measured intraluminal pres sures below at and above the gastroesophageal junction with a no 14 Sawyer gastric tube equipped with a pressure-sensitive Gauer tip and electric connections As the tip was withdrawn from the stomach in 0 5 cm steps an abrupt change in the direction of the respiratory excursions marked the level of the hiatus In the gastric fundus 3 5 10 cm below the hiatal level end expiratory pressures averaged —5 7 +1 8 and +13 3 cm of water in the sitting supine and head-down (15 degree) position respectively Drinking 250 ml barium suspension in the head down position did not change fundic pressures appreciably

On moving the pressure sensitive tip in small steps from the gastric cardia to the esophagus a 2 3 cm zone of high pressure was detectable with maximal pressures extending from 0 5 cm below to 0 5 cm above the hiatus Pressures in this zone were higher in the supine than in the sitting posi tion suggesting that they vary to maintain a small but con stant excess over intragastric pressures At the end of in spiration the band was narrower and its pressure less than at the end of expiration

After a swallow pressure in the high pressure zone began to fall 1 5 2 5 seconds reached a nadir in 2-6 seconds and then with arrival of the esophageal peristaltic wave 6-10 seconds after deglutition again began to rise (Fig 82) At the upper end of the zone a phase of elevated pressure well above the resting level and lasting some 13 seconds fol lowed the fall in pressure but this phenomenon was less apparent at the lower end of the zone

(1) G stroe ter logia 86 135 150 1956.

matic hiatus rather than dealing with the intangible tone of a sphincter — Ed]

Relationship between Hiatus Hernia and Pregnancy Clin ical Study of 40 unselected pregnant women from an ob stetric clinic is reported by Leo H Siegel Herbert Greenfield and Edgar Kogan (Newark N J) The gastroesophageal junctional area was studied radiologically in each patient during the 4th and 8th months of pregnancy and if hernia was found at the end of the 1st postpartum week The pa tient first filled the stomach with barium suspension and then drank additional swallows of barium while films were obtained in the left and right anterior oblique and in a left posterior oblique Trendelenburg position Further study was avoided because of the danger of radiation hazards to the fetus

Seven hiatus hernias were discovered 2 being noted in the 4th month and all 7 disappearing post partum The symp tomatology was too indefinite to warrant analysis

A 17% incidence of hiatus hernia is considerably higher than the 5% incidence in the general population On the other hand the finding of 2 (and possibly 3) hernias in the 4th month suggests that these patients may have had hernias anyhow or that production of hernia during pregnancy is not determined only by uterine size Since all hernias dis appeared post partum they were probably related to the pregnancy Although multiparas should theoretically be more prevalent in a group of pregnant women with hiatus hernia such was not the case

► [X rays in pregnant women are becoming rarer and rarer hence these studies present necessarily limited but valuable data If further follow up were possible it would be nice to know whether those with transient her nias in pregnancy are the ones susceptible to spontaneous and permanent hernias later in life

The presence of diaphragmatic hernia in pregnancy is generally blamed for the heartburn so common in that state but the incidence of pregnancy hernia as reported here would hardly seem to account for the large number of pregnant women with heartburn An interesting alternative explanation proposed by a practicing obstetrician is that the same hor mone which may relax ureters and pelvic ligaments in pregnancy (relaxin) also affects the competence of the gastroesophageal barrier and in partic ular the tone of the lower esophageal sphincter —Ed]

✓**Clinical Evaluation of Tubeless Gastric Analysis** The azure A dye contained in Diagnex® Improved (a Squibb product with 45 mg azure A/Gm carboxylic cation

(2) Gast ent logy 3 479-482 M h 1957

These observations appear to indicate the existence of a physiologic sphincter at the gastroesophageal junction The sphincter remains in tonic contraction between swallows but relaxes promptly as part of the deglutition reflex about the time that peristalsis begins in the upper esophagus The adjustments of pressure that appear to take place in the supine position and in different phases of the respiratory cycle sug

Fig 8 —S m lt eo d g of pressur l w part f e ph (pl tw t c gs) a d j t onal ph ct (l we trac g) d g d gl t t f ll p u t ph te ly d glut t on seq n e F co d g w m de 3 t ans lu e s c t d to fi e ope t pped polyethyle e t b wall w d by th ubject (C t y f Fyk F E J t al G t oe te ol gia 86 135 150 1956)

gest that pressure within this sphincteric zone is maintained above gastric pressure in the face of circumstances which might appear to favor reflux

► [The attempt to demonstrate an intrinsic physiologic sphincter at the lower end of the esophagus is about 100 years old The degree however to which physicians have believed in this sphincter has fluctuated like the stock market With the publication of this exquisite study from Codes laboratory sphincter stock may be expected to go up in lively fashion but surgeons will not buy heavily The trouble is that the exact contribution of the intrinsic sphincter in preventing gastroesophageal reflux is still a matter of debate Within the past 3 years as a matter of fact 2 articles *emanating from the same institution reached diametrically* opposite conclusions as to the roles of the lower esophageal sphincter and the diaphragm in controlling reflux (Proc Staff Meet Mayo Clin 29 399 1954 Surgery 39 901 1956) Until the situation is more settled surgeons will continue to treat reflux by attacking the concrete shape of the diaphrag

intubation were also correctly identified by the tubeless test

The tubeless test is reliable Only 1 patient showed apparent sensitivity reaction—costovertebral angle pain which cleared in 24 hours without any other evidence of renal disease The test requires further evaluation in severe renal disease gastric obstruction diarrhea and malabsorption but will probably prove to be undependable in these situations

► [Diagnex® Improved is not on the market at the moment of writing but i promised soon By and large its particular usefulness would appear to be in the screening of large numbers to find those with achlorhydria For study of the individual patient the gastric tube should not be discarded it is really not so fearful an instrument as to require circumvention at the expense of direct and quantitative measurement of gastric acidity —Ed]

✓Effect of Reserpine on Basal Gastric Secretion in Man was studied by Joseph B Kirsner and Harold Ford[4] (Univ of Chicago) Basal acid secretion was measured for 2 hours in the morning with 3 control studies before drug administration Reserpine was then taken orally by 8 reliable volunteers on a schedule of 0 1 mg 4 times daily (1 week) 0 25 mg 3 times daily (1 week) and 0 25 mg 4 times daily (10 weeks) Gastric analyses were repeated at the end of the 3d 5th 7th 9th 11th and 12th weeks after the start of drug intake with 2 analyses 2 and 4 weeks after discontinuation of the drug Acid production was unaffected in 7 of the 8 subjects In 1 volume was unchanged but acid concentration rose significantly

Reserpine intravenously (1 2 5 mg total dose) was given over 30 minutes following a 1 hour control period with gastric analyses continued for 3 6 hours Gastric secretion was increased in all normal subjects (4) and in those with gastric (2) or duodenal ulcer (5) The magnitude of elevation varied among individuals but was unrelated to presence or absence of ulcer Gastric secretion in 5 patients with gastroenterostomies and vagotomies was unaffected by insulin induced hypoglycemia but increased in response to reserpine intravenously in a manner similar to that in normals and ulcer patients

Effects of single intravenous doses of ACTH (20 units) hydrocortisone (50 mg) and reserpine (1 5 2 mg) were compared in three separate tests in each of 5 patients Corticotropin produced no consistent rise and hydrocortisone stim

(4) A M A A h I t Med 99 390 400 March 1957

exchange resin) is readily displaced by acid in the stomach and thus made available for absorption and renal excretion Because of the simplicity of the test Robert J Bolt Theodore G Ossius and H Marvin Pollard[3] (Ann Arbor Mich) evaluated the usefulness of this compound as a tubeless method for assessing free gastric acidity

The test was performed in 193 patients 90 of whom were also tested with gastric intubation and histamine stimulation The tubeless test was performed according to the following directions (1) Do not eat after midnight (2) Void and discard morning urine (3) Eat no breakfast drink one half glass water containing 0 5 Gm powdered caffeine sodium benzoate (4) Void 1 hour later and save urine in bottle marked control (5) Drink one fourth glass water containing Diagnex® Improved do not chew granules but wash down with another one fourth glass water (6) Void after 2 hours and save entire quantity in bottle marked urine sample

Presence of azure A was detected by comparing the color of the urine sample with that of control both diluted with water to 300 ml If no blue color was observed 10 ml aliquots of the diluted samples were boiled for 10 minutes and then compared If results were still doubtful the boiled aliquot was compared with standards and the blueness judged as follows deeper than 0 6 mg /300 ml standard—free acid present 0 3 0 6 mg /300 ml standard—borderline free acid less than 0 3 mg /300 ml standard—achlorhydria

After step 1 129 (67%) of the urines were blue after step 2 42 (21%) and 8 (4%) were positive when compared with 0 6 mg standard Thus 179 (93%) of the 193 had free acid by this test 13 (6 7%) had achlorhydria—no color or a color less intense than the 0 3 mg standard—and 1 excreted unidentifiable pigments

Free acid was present in 80 (89%) of the 90 tested by direct gastric analysis Of this group 76 (95%) were properly identified by the tubeless test 4 of the 76 were in the borderline group by the tubeless method (between 0 3 0 6 mg standards) Of the 80 known acid secretors 3 (3 8%) 1 of whom had had a subtotal gastrectomy failed to show acid by the tubeless test The 10 patients with achlorhydria by gastric

(3) G troent r logy 3 34-40 Ja ary 1957

intubation were also correctly identified by the tubeless test

The tubeless test is reliable Only 1 patient showed apparent sensitivity reaction—costovertebral angle pain which cleared in 24 hours without any other evidence of renal disease The test requires further evaluation in severe renal disease gastric obstruction diarrhea and malabsorption but will probably prove to be undependable in these situations

► [Diagnex® Improved is not on the market at the moment of writing but is promised soon By and large its particular usefulness would appear to be in the screening of large numbers to find those with achlorhydria For study of the individual patient, the gastric tube should not be discarded it is really not so fearful an instrument as to require circumvention at the expense of direct and quantitative measurement of gastric acidity —Ed]

✓Effect of Reserpine on Basal Gastric Secretion in Man was studied by Joseph B Kirsner and Harold Ford[4] (Univ of Chicago) Basal acid secretion was measured for 2 hours in the morning with 3 control studies before drug administration Reserpine was then taken orally by 8 reliable volunteers on a schedule of 0 1 mg 4 times daily (1 week) 0 25 mg 3 times daily (1 week) and 0 25 mg 4 times daily (10 weeks) Gastric analyses were repeated at the end of the 3d 5th 7th 9th 11th and 12th weeks after the start of drug intake with 2 analyses 2 and 4 weeks after discontinuation of the drug Acid production was unaffected in 7 of the 8 subjects In 1 volume was unchanged but acid concentration rose significantly

Reserpine intravenously (1 2 5 mg total dose) was given over 30 minutes following a 1 hour control period with gastric analyses continued for 3-6 hours Gastric secretion was increased in all normal subjects (4) and in those with gastric (2) or duodenal ulcer (5) The magnitude of elevation varied among individuals but was unrelated to presence or absence of ulcer Gastric secretion in 5 patients with gastroenterostomies and vagotomies was unaffected by insulin induced hypoglycemia but increased in response to reserpine intravenously in a manner similar to that in normals and ulcer patients

Effects of single intravenous doses of ACTH (20 units) hydrocortisone (50 mg) and reserpine (1 5 2 mg) were compared in three separate tests in each of 5 patients Corticotropin produced no consistent rise and hydrocortisone stim

(4) A M A A h I t. Med 99 390-400 M ch 1957

ulated secretion in 1 patient and produced a drop in acid in another Tremendous rises in volume and acidity were evoked in all 5 patients by reserpine Blood pressure de creased slightly for 2-4 hours after reserpine injection and most patients experienced generalized warmth and flushing for 1 2 hours This was frequently accompanied by a vascu lar type headache clinically similar to histamine headache No eosinopenia was demonstrated in 3 patients before and 2-4 hours after reserpine intravenously

The unequivocal action of reserpine intravenously on gas tric secretion does not appear to be mediated via the adrenal cortex The mechanism of action of reserpine is unknown but it generally appears to augment parasympathetic activ ity Thus part of its gastric secretory effect may be through the vagus but the secretory effect in vagotomized patients indicates that the vagal mechanism is not essential A periph eral action possibly through release of intracellular stores of histamine is apparent

These studies indicate that reserpine in oral doses up to 1 mg daily may be administered with little stimulation of gas tric secretion or hazard of precipitating peptic ulcer Larger oral doses should be given cautiously to ulcer patients and intravenous use of reserpine avoided

► [Wolf and Rossman (Am J Gastroenterol 25 430 1955) agree in general but find that larger oral doses of reserpine 2 5 mg do increase gastric acidity somewhat Neither they nor Kirsner and Ford anticipate gastroduodenal disorders as a result of giving small doses of reserpine for a long time and Drenick (Am. J Digest Dis 1 521 1956) actually used 0 75 mg reserpine daily in treating 12 patients with acid peptic dis orders with what were interpreted as beneficial results

On the other hand 3 acute duodenal ulcers (Gastroenterology 31 500 1956) and 5 ulcers complicated by hematemesis and melena (A M A Arch Int Med 99 218 1957 New England J Med 255 1193 1956) have been reported as occurring during reserpine therapy The important point is that 7 of these cases were schizophrenics receiving 3 mg or more of the drug per day One was a hypertensive receiving along with other drugs less than 1 mg reserpine daily

A consistent pattern seems to emerge with less than 1 mg of reserpine taken daily there is little danger of inducing peptic ulceration with larger doses some caution must be exercised —Ed.]

Duodenal Ulcer and Hypophysis Adrenal Stress Mecha nism Herzl Ragins Lester R Dragstedt II John H Lan dor Edwin S Lyon and Lester R Dragstedt[5] (Univ of Chi cago) studied the total volume and hydrochloric acid con tent of gastric juice in Heidenhain pouches of healthy fast

(5) Surgery 40 886-893 November 1956

ing dogs receiving insulin stress epinephrine ACTH and adrenocortical hormones

Intravenous doses of 10 20 and 100 units of regular insulin failed to produce any secretion of acid although the large doses induced severe weakness and lethargy and depressed blood sugar below 28 mg/100 ml Secretions were collected for 7 9 hours in anticipation of an extravagal delayed response but none was found Epinephrine 3 mg subcutaneously ACTH 40-80 USP units subcutaneously cortisone 200 mg intramuscularly and sodium hydrocortisone hemisuccinate 66 8 mg intravenously did not produce secretion of gastric acid To prove that the preparations were capable of responding to humoral stimuli 1 mg histamine base was administered subcutaneously Intense secretion of hydrochloric acid resulted in each case

The extravagal theory of gastric acid secretion postulates that a stress situation leads to hypothalamic stimulation via cerebral pathways or epinephrine release The hypothalamus in turn is believed to stimulate the anterior pituitary to release ACTH which acts on the adrenal cortex to secrete adrenocortical steroids These are supposed to act directly on the gastric secretory cell If this mechanism operates the hypoglycemic stress produced by insulin should cause an early vagal secretion and a delayed extravagal secretion mediated by the postulated sequence of humoral agents No evidence was obtained however that hypoglycemic stress affected the secretion of a denervated and isolated gastric pouch which is an ideal preparation for studying secretory effects of humoral mechanisms It is concluded that exacerbation of peptic ulcer by ACTH and cortisone is probably not a result of increased gastric acid secretion

► [The argument continues unabated. To the bystander it seems that not enough attent on is paid to temporal relationships A sl ght change in the pH of a monkey s gastric contents produced immediately after a manipulation is interpreted as evidence for an adrenal mechanism (1954 55 YEAR BOOK p 474) Conversely failure to obtain secretory changes immediately after applying acute stress is taken as evidence against this mechanism Has it not been shown with some certainty that the most consistent effect of adrenal glycocort coids on gastric secretion is gradual developing slowing but progressively with prolonged exposure?—Ed.]

Etiology of Duodenal Ulcer I Relation of Specific Psychologic Characteristics to Rate of Gastric Secretion (Serum Pepsinogen) Duodenal ulcer may develop when an individual with high gastric secretory capacity (physiologic param

eter) and a relatively specific psychic conflict inducing tension (psychic parameter) is exposed to an environmental situation noxious to that particular individual (social parameter) To evaluate the role of each of these parameters in precipitating ulcer Herbert Weiner Margaret Thaler Morton F Reiser and I Arthur Mirsky[6] studied draftees exposed to the environment presented by the 16 week basic training period Gastric hyper and hyposecretors were selected from 2 073 draftees on the basis of serum pepsinogen levels The Cornell Medical Index the Saslow Screening Inventory and a sociologic rating scale were also applied to each man

Each week 20 subjects with the highest and lowest pepsinogen levels identified only by code number received a battery of psychologic tests (Rorschach Blacky Pictures and Draw A Person) a brief interview with a psychiatrist and social worker and a gastrointestinal x ray examination All but 13 of the initial group of 120 so studied were re examined psychologically and by x ray 8 16 weeks later Sixty three of the subjects were hypersecretors their pepsinogen levels were within the highest 15% of the values obtained in the entire group of 2 073 the hyposecretor group had levels falling within the lowest 9% Ulcer disease was identified in 4 subjects on the initial x ray and active ulcers were found in 5 others on repeat examination All 9 were hypersecretors according to pepsinogen tests

The psychologic material was evaluated without knowledge of the pepsinogen values to determine if hypersecretors could be separated from hyposecretors and proneness to ulcer identified To select hypersecretors expected to show intense infantile oral dependent wishes immaturity, tendency to please and difficulties revolving about oral impulses and hostility the test material was examined for oral symbolism (talking kissing etc) responses referable to heat and cold diffuse anxiety depressive associations and drawings with primitive gross or asexual characteristics Hyposecretors expected to show pseudomasculine defenses and paranoid trends were identified on the basis of material showing little or no oral depressive or anxiety content and little indication of a need to please

On the basis of the postulated psychologic traits rated by 3 observers 61% of the 120 subjects were placed in the correct

(6) Psychosom Med 19 1 10 Jan Feb 1957

groups 71% of the hypersecretors and 51% of the hyposecretors Ulcers were suspected in 10 subjects on the basis of intense psychologic and hypersecretor characteristics Seven of these 10 were in the ulcer group and 2 were hypersecretors Retrospective study showed that all 9 with ulcers had been correctly identified as hypersecretors by psychologic testing No criteria separated the ulcer group from other hypersecretors other than the intensity of the attempt to maintain good personal relations

Although no single psychologic criterion separated the hypersecretors from the hyposecretors with an accuracy of more than 64 2% all 20 together separated the two groups with an accuracy of 85% No explanation is available for this remarkable correlation between serum pepsinogen concentration and specific personality characteristics Since serum pepsinogen levels at birth show a normal distribution with some newborns having values higher than those in ulcer patients psychologic characteristics are probably not responsible for the physiologic state of the stomach

► [Certain aspects of this fascinating study may raise the dubious eyebrow Can the person with increased gastric secretory capacity and work hypertrophy of the parietal cells (1955 56 YEAR BOOK p 482) really be identified by a single randomly obtained measurement of serum pepsinogen content? And do ulcer patients as a group really draw primitive gross or asexual faces? Nevertheless to the infidel observer this appears as a milestone in the psychiatric literature Instead of the usual practice of finding that known ulcer patients have this or that characteristic postulated characteristics of the ulcer patient have been used—successfully—to identify the ulcer patient Moreover psychologic and physiologic variables manipulated without prejudice or forehand knowledge have been shown to exhibit a positive correlation A few more studies like this and especially if the physiologic data are better supported may force the infidel to join the ranks of the faithful —Ed]

Peptic Ulcer Near the Pylorus This lesion has been said to produce an atypical ulcer syndrome To evaluate this claim William T Foulk Mandred W Comfort Hugh R Butt Malcolm B Dockerty and Harry M Weber[7] (Mayo Clinic and Found) analyzed the records of 132 patients with subtotal gastric resection for an ulcer at or near the pylorus As no well defined anatomic pyloric channel exists 3 groups were selected from the 132 according to the site of ulceration 35 channel ulcers in a zone extending 2 cm above the gastroduodenal mucosal junction 29 pyloroduodenal ulcers straddling the junction and 19 duodenal ulcers near the pylorus Symptoms and findings in these groups were compared

(7) Gastroent 32 395-403 March 1957

eter) and a relatively specific psychic conflict inducing ten sion (psychic parameter) is exposed to an environmental situation noxious to that particular individual (social param eter) To evaluate the role of each of these parameters in precipitating ulcer Herbert Weiner Margaret Thaler Mor ton F Reiser and I Arthur Mirsky[6] studied draftees exposed to the environment presented by the 16 week basic training period Gastric hyper and hyposecretors were selected from 2 073 draftees on the basis of serum pepsinogen levels The Cornell Medical Index, the Saslow Screening Inventory and a sociologic rating scale were also applied to each man

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(6) Psychosom Med. 19 1 10 J Feb 1957

objective evidence that their action is deleterious Fifty patients with active gastric or duodenal ulcer were maintained on a routine ulcer regimen including diet interval feedings antispasmodics and antacids and in addition were given a capsule containing a spice three times daily with meals Spices tested included cinnamon nutmeg allspice mace thyme sage paprika caraway seed chili pepper cloves black pepper and mustard seed in doses used in well seasoned recipes The spices were given for 3 180 days usually 25 50 days

Three patients had mild symptoms such as sourness or heartburn in 2 receiving black pepper the spice had to be discontinued because of epigastric pain and nausea With these exceptions the spices did not affect ulcer healing as judged clinically and radiologically

Eight patients with inactive duodenal ulcer were given no treatment except a moderate bland diet with a spice capsule with each meal One patient had belching when he took cloves a second had severe symptoms when given black pepper

In 15 patients with various disorders gastroscopy was done before and 10 minutes after a watery suspension of cinnamon nutmeg allspice thyme black pepper chili pepper cloves or paprika was instilled into the stomach in doses 2½ times the amount used in highly seasoned food No mucosal change was noted except moderate hyperemia after chili pepper and severe hyperemia after black pepper In 5 subjects given cinnamon nutmeg allspice and cloves for 21 55 days uropepsin secretion was unchanged

Spices if ingested with meals do not appear to retard ulcer healing or produce untoward gastric symptoms or reactions Exceptions are chili pepper and black pepper

► [More data like these are needed. Our books on dietotherapy are heavy with objective nutritional information but little except hand me downs and cultural phobias are responsible for some of the statements made concerning the effect of various foods on the gastrointestinal tract and its function See also page 552—Ed]

Alkali Requirement for Continuous Neutralization of Gastric Contents in Gastric and Duodenal Ulcer Different therapeutic regimens were given to 3 groups of ulcer patients by A V Price and P H Sanderson[9] (St Mary s Hosp London) to evaluate their effectiveness in maintaining gas

(9) Clin. Sc 15 285 295 May 1956

with those produced by ulcers higher in the stomach and lower in the duodenum

Pain was the commonest complaint in all groups Atypical location of the pain was recorded in all groups but no more frequently for one ulcer site than another Relief from pain achieved by food and alkali was commonly noted in all groups particularly in those with frank duodenal ulcer Nausea and vomiting were noted with about the same frequency in patients with ulcers near the pylorus less commonly in those with unequivocal gastric or duodenal ulcers Nausea and vomiting were often signs of gastric obstruction but patients with pyloric channel ulcers had a 65% incidence of nausea and vomiting and only a 29% incidence of gastric obstruction Weight loss was noted by about 50% of patients with gastric, pyloric channel and pyloroduodenal ulcers in frank duodenal ulcers it occurred about half as often When over all evaluation of the history was attempted atypical ulcer histories were found associated with various ulcer sites as follows frank duodenal 6% duodenal near pylorus 11% pyloroduodenal 28% pyloric channel 28% and gastric 17%

Radiologic localization of ulcers near the pylorus was often inaccurate In particular 8 duodenal and pyloroduodenal ulcers were reported as prepyloric thus suggesting to the clinician a connotation of possible malignancy

A clinical syndrome sufficiently distinct to permit diagnosis of pyloric channel ulcer was not found and the authors recommend that the term be dropped in favor of the simpler designation of ulcer at or near the pylorus

► [In a rebuttal (Gastroenterology 32 537 1956) Julian Ruffin points out that the conclusions of the Mayo group are hard to understand since their report seems to agree with his (J A M A 159 668 1955) that patients with ulcers near the pylorus have a greater incidence of nausea vomiting and weight loss than patients with classic duodenal ulcer It is probably a matter of emphasis From a statistical viewpoint the statement of the Mayo group that a pyloric channel ulcer does not present a syndrome sufficiently characteristic to permit diagnosis cannot be challenged particularly as it applies to their severe ulcer cases requiring surgery On the other hand *in individual patients presenting atypical histories* with nausea and vomiting and an initially negative or equivocal x ray report I have found Ruffin s points about pyloric channel ulcers most helpful in tracking down the correct diagnosis —Ed]

× Effect of Spice Ingestion on Stomach was studied by Max A Schneider Vincent DeLuca Jr and Seymour J Gray[8] (Boston) who felt that spices are often interdicted without

(8) Am J Gast nt rol 26 722 732 Decembe 1956

objective evidence that their action is deleterious Fifty patients with active gastric or duodenal ulcer were maintained on a routine ulcer regimen including diet interval feedings antispasmodics and antacids and in addition were given a capsule containing a spice three times daily with meals Spices tested included cinnamon nutmeg allspice mace thyme sage paprika caraway seed chili pepper cloves black pepper and mustard seed in doses used in well seasoned recipes The spices were given for 3 180 days usually 25 50 days

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(9) Cl S 15 285 295 M y 1956

tric acidity above pH 4 0 the level at which peptic activity is 5 10% of maximum In all cases gastric samples were aspirated at half hour intervals from 8 a m to 8 p m and at hourly intervals from 9 p m to 7 a m The position of the gastric tube was monitored by x ray and the acidity recorded with a pH meter

The first group consisted of 10 gastric and 19 duodenal ulcer patients on a modified Meulengracht diet without alkali given additional 6 oz milk feedings at 6 a m 10 a m

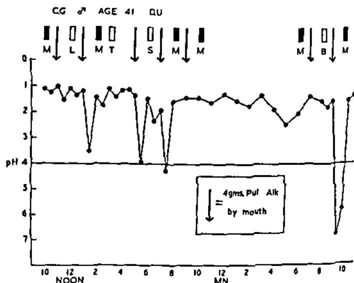


Fig 83—Twenty fou h u alys g in p t nt 41 with d oden l ulcer r c vi g nt rm tt nt lkal by m uth du g th d y (lkal n powd 4 Gm) (C rte y f P ce A V and S de on P H Cl Sc 15 285 295 M y 1956)

2 p m 8 p m and 10 p m The second group consisted of 5 gastric and 5 duodenal ulcer patients similarly treated with the addition of 4 Gm alkaline powder at 7 a m 9 a m 11 a m 1 p m 5 p m 7 p m and 9 p m The third group also on a modified Meulengracht diet consisted of 15 gastric and and 15 duodenal ulcer patients given via a second tube a continuous intragastric drip of milk (60 ml /half hour) containing known amounts of sodium bicarbonate

The gastric ulcer patients in group 1 usually showed a pH rise after meals with a tendency toward spontaneous nocturnal neutralization while the duodenal ulcer ients gen

erally had higher acid levels with less pH rise after meals and a continuous low pH during the night Acidity was partially controlled in the gastric ulcer patients in the second group but less so in the duodenal ulcer patients in whom the nocturnal acid plateau was unchanged (Fig 83)

The pH could be kept at 4 0 or above in all but 2 of the gastric ulcer patients in the third group with 60 Gm or less sodium bicarbonate/24 hours Most of the duodenal ulcer patients required 80 or 100 Gm /24 hours (range 60 140 Gm) for similar control If it is assumed that complete mixing and neutralization of all the ingested alkali occurred the duodenal ulcer patients secreted up to 1 900 mEq acid daily and rarely less than 715 mEq Since the upper limit of gastric acid concentration is 160 mEq /L the calculated daily volume of gastric juice was 4 5 12 1 L Even if only one half the ingested alkali was required for neutralization the calculated volume of secretion was still large Other authors using similar methods have also calculated gastric secretory rates of 4 4-6 8 L /day

The continuous drip treatment was well tolerated for periods up to 3 weeks and caused marked symptomatic relief even in patients not previously relieved on conventional hospital treatment To afford relief the sodium bicarbonate content had to be adjusted individually to control the pH

► [A few years ago the same authors showed that patients with duodenal ulcer could tolerate doses of up to 140 Gm. sodium bicarbonate daily for 3 weeks without untoward effects (1955 56 YEAR BOOK p 499) Now they show that doses almost as large are necessary if gastric pH is going to be controlled throughout the 24 hours in patients with duodenal ulcer Most of us however compromise with the exigencies of reality and treat our ambulatory ulcer patients with a regimen not expected to control gastric pH at all times We say this is sufficient to induce healing by clinical and radiologic criteria but one disturbing thought remains if in treating an early ulcer case a more continuous control of gastric acidity were achieved would we decrease the distressingly high number of recurrences? Ulcer recurrence however would also seem to be common in England where intragastric drip methods of ulcer therapy appear currently more popular than in the United States —Ed]

Prolonged Anticholinergic Therapy of Duodenal Ulcer Medical treatment even by diet alone usually affords prompt and complete relief in uncomplicated duodenal ulcer The outlook for permanent cure however is unfavorable and there is general agreement that 44% will recur within 1 year and 74% within 2 years There are few reported studies to determine whether continuous medical treatment will af

fect these figures David Cayer[1] (Bowman Gray School of Medicine) used the double blind technic to study the effects *of anticholinergic drugs given continuously to 116 patients* with uncomplicated active duodenal ulcer over 7 13 (average 10 5) months

The 111 men and 5 women aged 22 58 had had an average of 2 8 recurrences yearly over a mean period of 8 2 years 23 had a history of hemorrhage and 9 had had perforations Av erage daily doses of 400 mg Banthine® 120 mg Pro ban thine® 200 mg Pathilon® 1 6 mg atropine or a placebo were administered The patients were also advised to take antacids and a bland diet with 6 daily feedings

Freedom from ulcer distress throughout observation or improvement despite periodic recurrences was noted in 75% of the patients receiving Banthine® or Pathilon® and in half of those receiving placebo atropine or Pro banthine® These differences were statistically significant Fewer recur rences or none developed in 75% receiving Banthine® or Pathilon® in 60% receiving atropine or Pro banthine® and in 50% receiving placebo These differences were not signifi cant Only 19% of patients taking anticholinergics were asymptomatic during the period of study Bleeding appeared *in 11% of those receiving synthetic anticholinergic drugs* and in 5% receiving atropine or placebos but again the difference was insignificant Pyloric obstruction developed in 1 person receiving an anticholinergic agent No obvious cause for re currence was found in most cases and there was no relation between rigidity of diet and recurrence The development of poor and irregular eating habits seemed to be a more impor tant factor

The data suggest that ulcer patients maintained on ade quate therapeutic regimens including synthetic anticholin ergic drugs fare better than those receiving similar therapy without anticholinergics or plus atropine in the dosage noted It is equally apparent that anticholinergic drugs do not prevent recurrences or reduce the incidence of compli cations

Antigizzard Ulcer Factors in Treatment of Gastric Ulcer in Man were reviewed by Erling Lund[2] (Copenhagen) Dam and associates produced gizzard ulcers in chicks by adminis

(1) Am J D gest D s 1 301 309 J ly 1956
(2) D sh M B ll 3 187 Septembe 1956

tering an artificial diet The addition to the diet of hog liver calf brain or various extracts of these organs afforded marked protection against the ulcers

On the basis of these studies attempts have been made to treat human peptic ulcer with preparations of antigizzard ulcer factors One preparation contains dehydrated cream and milk vitamins and iron in addition to nonsteridic extracts of cattle organs and is marketed in the United States and Canada under the name of Exul or Nupra Sensational claims for this product have appeared in the lay press To evaluate these claims two clinical trials in groups of 152 and 36 patients with gastric and duodenal ulcers were performed in Denmark In each study half the patients received antigizzard ulcer factors and half did not but in other respects all were treated with identical dietetic measures Both studies showed that the same results occurred whether or not the antiulcer preparations were given Thus no specific curative effect was demonstrated

► [The vast publicity given to the agent here discussed on TV and in national magazines (that wonderful new medicine which is curing all the ulcers up in Canada but which we are not allowed to have) drove swarms of patients to ask their doctors about it I for one had no good answer to given them until this brief report became available Obviously diets are intolerable and the search for some simple pill or injection to control ulcer continues (1954 55 YEAR BOOK, p 494 and 1955 56 p 500) —Ed]

Observations on Value of Gastric Irradiation in Treatment of Duodenal Ulcer are presented by Erwin Levin Charles B Clayman Walter L Palmer and Joseph B Kirsner[3] (Univ of Chicago) in 723 patients followed for 5 18 years All had symptoms severe enough to warrant hospitalization but those requiring immediate surgery because of high grade pyloric obstruction perforation or uncontrollable hemorrhage were excluded With these criteria the series included more therapeutic problems than the usual ambulatory group Accepted routines of medical management were used besides irradiation because the effect of the latter on gastric secretion is variable in degree and duration Hence irradiation was used as an adjunct to conventional management

The table shows the technics used and the respective recurrence rates Of the 332 recurrences (46%) 126 occurred within 12 months of treatment Recurrence rates/100 patient years decreased from 102 before to 17 after therapy

(3) G t oente l gy 32 42 50 J ry 1957

with the latest technics a reduction of 83% Deceased patients were analyzed separately but the recurrence rate was similar Hemorrhage before therapy of 4 3/100 patient years *fell to 1 1 after therapy a reduction of 75%* For deceased patients the fall was 48%

Gastric secretion by the standard histamine test decreased by more than 50% 2 4 weeks after irradiation in 36% of the patients Histamine achlorhydria developed in 12% but was usually transient Ulcer recurrences invariably were preceded by a return of gastric acid

Eight patients (1%) died of ulcer complications There were 32 cancer deaths 4 were gastric cancers 2 being pres

TECHNICS OF IRRADIATION

Tech q	Y	N Tre m t pe P rtal	D ion f Trea m t	P rtal	C ec Dose G F ndus	P l ts N	Rec rrences	
							T J 1 36	5 years
			d y	m			%	
I	1937	5-6	12 14	15 x 15	2900-3600	70	74	54
				20 x 20				
II	1938	3	6-7	13 x 13	661 987	24	58	46
				15 x 15				
III	1939-43	5-6	11 12	13 x 13	1100-1500	297	46	30
IV	1944-47	5-8	11 14	13 x 13	1600-1700	207	43	29
V†	1948 50	5 8	12 14	13 x 13	1600 1700	125	32	30

In t h es I a d II dosage is mea ured in air wh l depth do ge is appl d to te hn III V
†Outl of st mach ma ked under fl oroscop c observation f om th s d te o

ent at irradiation and 2 developing afterward Three of 4 carcinomas of the pancreas appeared after therapy One patient died of carcinoma of the duodenum and 1 with portal cirrhosis died of carcinoma of the liver In 11 patients (1 5%) gastric ulcer developed a rate less than the expected incidence of gastric and duodenal ulcer in the same patient Side effects were negligible except for transient nausea and tanning of the skin at the treatment sites No leukemia or aplastic anemia occurred

► [These figures make it difficult to escape the conclusion that gastric irradiation should be offered to the patient with severe ulcer disease who for one reason or another is not a candidate for surgical treatment. As the next abstract suggests moreover improved technical facilities may make this type of therapy even more satisfactory —Ed]

Cobalt 60 Teletherapy for Complicated Peptic Ulcer

Charles H Brown and Robert A Hays[4] used a cobalt-60

(4) Cl l d Cl n Q art. 24 17 5 J ary 1957

teletherapy unit (equivalent to a 3 000 000 volt x ray machine) to treat 11 patients with duodenal 3 with marginal and 1 with gastric ulcer The outline of the upper two thirds of the stomach determined by fluoroscopy was drawn on the body anteriorly and posteriorly and 300 r given to the skin of each of these two fields daily for 6 8 days About half the total dose 1 600 2 000 r was delivered to the stomach No skin reactions resulted although a similar amount of conventional roentgen irradiation would have caused mild erythema

The patients presented difficult and long standing problems in ulcer management and would as a rule have been treated surgically had not various contraindications existed After irradiation and conventional medical management all became asymptomatic for the 2 16 months of follow up Gastric acidity stimulated by histalog decreased from 32 to 100% of control values in 13 patients tested 3 9 weeks after irradiation Radiologic evidence of healing was also satisfactory Twelve patients had no side effects 3 had minimal nausea but no vomiting

Because it seems that irradiation with cobalt 60 is effective and better tolerated than conventional roentgen treatment its further ancillary use in the medical management of difficult ulcer cases is suggested

Melena and Hematemesis Follow up Investigation with Special Reference to Bleeding of Unknown Origin Gunnar Birke and Lars Engstedt (Karolinska Hosp Stockholm) studied the fate of patients with gastrointestinal hemorrhage in whom the first hospital work up (including radiography proctoscopy and hematologic tests) failed to reveal the cause of bleeding

Among 1 252 medical inpatients with gastrointestinal bleeding seen over 10 years the cause was determined at the first admission in 1 061 Distribution of causes was ulcer (gastric duodenal or anastomotic) 30% ulcerative colitis 25% malignant tumor 9% liver cirrhosis 4% blood diseases 4% Other etiologic disorders include gastritis acute yellow atrophy and hemorrhoids Diverticula anywhere in the gastrointestinal tract were never found to be a cause of bleeding

In 191 patients 15% of the entire group no definite etiology

(5) G t oe t logi 85 97 115 1956

was established during the initial admission for bleeding Follow up was not possible in 8 All others were followed by readmission autopsy report other hospital protocol or questionnaire for 4 14 years Eighty six patients (45%) remained completely symptom free The initial hemorrhage in these patients was apparently an isolated episode without later significance In 9 patients (5%), further bleeding occurred but reinvestigation including 3 exploratory laparotomies in 1 patient and autopsy in another failed to reveal the source

In 88 (46%) of these patients the cause of the initially unexplained bleeding was later found The causes in this group were ulcer (gastric duodenal or anastomotic) 49 benign tumor 6 malignant tumor 24 other causes 9 Peptic ulcer was thus found to be the cause of bleeding in 26% of those with initially unexplained hemorrhage It was diagnosed by repeat roentgenography in 31 cases laparotomy in 13 and autopsy in 5 Cause of hemorrhage was initially undetermined in 14% of all bleeding due to gastric ulcer 9% of that due to duodenal ulcer and 26% of that due to anastomotic ulcer

Malignant tumors caused bleeding in 13% of the group initially undiagnosed These were diagnosed by operation or autopsy Routine clinical examination thus failed to detect malignant tumor as the cause of alimentary tract bleeding in almost 2% of the 1 252 patients studied Carcinomas of the stomach or colon were missed at the initial bleeding episode in 11 and 14% respectively Three cases of bleeding carcinoma of the duodenum and ampulla of Vater and 7 of 21 carcinomas of the pancreas were not diagnosed initially

► [The excellent follow up system possible in Scandinavian countries pays off in studies such as this It has always been suspected that certain gastrointestinal hemorrhages are isolated episodes without later significance but it is nice to have a study not only confirming this suspicion but showing that about one half the cases with initially unexplained gastrointestinal hemorrhage fall into this category In another recent study (Gastroenterology 32 528 1957) 12 cases are reported in which organic causes were ultimately found to account for initially unexplained gastrointestinal hemorrhage. These however were selected cases chosen to illustrate a point. The Swedish report gives a broader perspective of the ultimate fate of patients with that all too-frequent problem acute gastrointestinal bleeding from an unidentified source —Ed.]

Bleeding Peptic Ulcer Clinical Study of 511 Cases is reported by Arne Aldman and Sten Wallensten[6] (Stockholm) From 1942 to 1953 3 879 peptic ulcers were treated at Sera

(6) Acta med. scandi av 155 205 222 1956

fimer Hospital and 511 (13%) of these presented manifest hemorrhage a figure lower than usual because cases of slight bleeding were eliminated Since gastric ulcers comprised 32 7% of all ulcers and 31 5% of bleeding ulcers gastric and duodenal ulcers bled with equal frequency

Patients were divided into groups with severe and slight hemorrhage depending on whether the hemoglobin was be low or above 50% and the red blood cell count below or above 2 000 000 The distribution of slight and severe hemorrhage was similar at all ages although there was a tendency toward severer bleeding in the older patients particularly those with gastric ulcers Nearly two thirds of those with history of ulcer for less than a year had severe hemorrhage less than half of those with longer histories had severe hemorrhage Age type and duration of ulcer undoubtedly determined the seriousness of the bleeding to a degree but not enough to provide a basis for reliable prognosis Repeated blood counts and the condition of the patient appeared to offer more valu able aid

X ray examinations were done as early as possible to make a diagnosis and choose appropriate therapy Among the 57 patients x rayed on admission a duodenal or gastric niche was seen in 41 X ray examination was noncontributory in only 6 instances and in no case did it lead to complications

Conservative treatment consisted of the Meulengracht regimen with frequent meals from the outset A change in the use of blood replacement took place during the investiga tion During the first 3 years 19 of 67 patients on the medical and 7 of 15 on the surgical service received transfusions during the last 3 years corresponding figures were 85 of 125 and 32 of 45 Thus in the last period 117 of 170 patients re ceived 252 L of blood Immediate partial gastrectomy was performed in only 22 patients in whom bleeding after gen erous transfusions continued to be life threatening In 20 others it was contemplated but bleeding ceased

Total mortality was 4 9% In severe hemorrhage it was 7 8% and in severe hemorrhage in the 7th and 8th decades 13 6 and 27% respectively The higher mortality rate in gas tric ulcer (7 95%) as compared with that in duodenal (3 3%) was also probably related to age With respect to the chang ing use of blood transfusions mortality was 7 4% in the first and 3 1% in the last period a reduction undoubtedly due to

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(6) Acta med. scandi av 155 205 22 1956

section is good therapy for the bleeding duodenal ulcer patient? Although additional and qualifying data might modify this impression the results as reported are indeed disappointing and challenging —Ed.]

Serum Calcium Levels in Unrecognized Perforated Peptic Ulcer The determination of serum calcium has been pro posed as a means of differentiating acute lesions of the abdo men from acute pancreatitis since lowered levels have been reported in as many as 70% of patients with moderate to se vere pancreatitis W J Snape and R S Naden Jr[8] (Cam den N J) report 2 cases of proved perforated peptic ulcer with low levels of serum calcium in 1 this finding delayed appropriate therapy

CASE 1—Man 37 had had episodes of nausea vomiting and in digestion for years and may have passed black stools One day he felt nauseated and suddenly experienced pain posteriorly at the root of the neck Pain and vomiting persisted until hospitalization On examination there were signs of shock and the abdomen was mod erately tense and tender in the upper quadrants Peristalsis was absent but there were signs of shock and the abdomen was mod was positive for occult blood The hematocrit value was 55% and the white blood cell count 23 000/cu mm Roentgenograms showed generalized abdominal haziness but no free air under elevated dia phragms On the 4th day the serum amylase level was 215 units/100 ml and the serum calcium level 6 4 mg /100 ml He improved on medical management and exploration was done on the 9th day Gen eralized peritonitis and a partially sealed off acute perforated duodenal ulcer were found

CASE 2—Woman 59 had dyspepsia for several years Early one morning she had acute stabbing pain in the right lower abdominal region for 15 minutes and later that day became dyspneic and cy anotic On hospitalization she was in shock Slight tenderness in the right lower quadrant was the only physical finding in the abdomen The rectum contained black stool which tested positive for blood The white blood cell count was 3 450/cu mm. and the hemo globin value 15 Gm /100 ml The next morning the serum amylase level was 135 units/100 ml and the serum calcium level was 6 9 mg / 100 ml Acute renal failure abdominal distention and a grayish blue mottled periumbilical cyanosis developed and she died Autopsy showed an acute perforated duodenal ulcer a chronic posterior duodenal ulcer and mild hyperemia of the pancreas liver, spleen kidneys and lungs

Perforated ulcers usually are recognized early in the course of the disease and serum calcium levels are not deter mined routinely This accounts for the lack of previous rec ognition of the correlation of depressed serum calcium levels and perforated ulcer The mechanisms by which serum cal

(8) Am J D g t. D 1 507 511 1956

blood replacement and timely surgical intervention when hemorrhage could not be controlled

► [This article was abstracted for two reasons In the first place it shows that the problem of bleeding ulcer in Swedish and American hos pitals is quite comparable More important however is the information it brings to bear on the usefulness of blood transfusions A small but insistent minority in the United States seriously question whether trans fusions are helpful in managing the bleeding ulcer patient and Snapper (Am J Gastroenterol 26 154 1956) even states that an over all fatality of all gastrointestinal hemorrhage of not above 2% before 1927 has now reached astronomical figures of 10 20% because of overenthusiastic use of transfusions in our large hospitals Perhaps the Swedish doctors were judicious in their use of blood In view of the small number of emergency operations performed it seems reasonable to credit the reduced mortality achieved over the years to the increased use of transfusions —Ed]

Medical Versus Surgical Management for Complication of Hemorrhage in Duodenal Ulcer was compared by Russel S Boles Jr William J Cassidy and Sara M Jordan (Lahey Clinic) to determine which offered the better long term prognosis Among 266 hospitalized patients with duodenal ulcer hematemesis or melena and present or impending shock medical management with a modified Sippy regimen was used in 141 and surgical management with subtotal gastrectomy in 125 Medical mortality was 2 1% surgical 1 6%

In the medical group 67 4% were treated for initial hem orrhage and 32 6% for recurrence During average follow up of 4½ years 26 9% subsequently bled in each category In the surgical group 29 6% were treated for initial hemorrhage and 70 4% for recurrence Average number of bleeding epi sodes before surgery was 3 Average follow up was 4 years and recurrence rates were initial group 10 8% recurrent group 17% and over all 15 2%

Of the patients with recurrent hemorrhage 47 4% bled within 3 and 71% within 5 years of medical therapy in the surgical group these percentages were 73 7 and 84 Thus re currences took place sooner after surgical than after medical management

In both surgical and medical management of bleeding duo denal ulcer history of previous bleeding has little prognostic value Recurrence rates with either form of treatment are disappointingly high

► [Furthermore if recurrent bleeding is indicative of recurrent ulcer do not the e figures seriously challenge the concept that subtotal gastric re

(7) Gastroenterology 32 52 59 January 1957

indeed In addition as the author points out it would constitute the only known case of biologic significance attributable to the effective optical activity of sugars Should this report be confirmed we may look forward to treating our dumpers with the low sugar high banana (fructose) diet used for so many years in the treatment of the celiac syndrome —Ed]

Potassium Exchange in Gastrojejunostomy was studied by H Baden C J Carlsen and H H Wandall[1] (Copenhagen) because a number of authors basing their opinion mainly on the finding of low serum potassium values have suggested that potassium deficiency is a cause of postoperative gastrointestinal paralysis The hypokalemia has been ascribed in turn to loss of intestinal juices and to adrenal activity stimulated by the stress of operation

Sodium potassium balance studies were made in 12 elderly patients with gastrojejunostomy for duodenal ulcer Postoperatively mild constant gastric suction was maintained until aspirated fluid was less than that ingested This was achieved in 7 with uncomplicated cases before the 5th postoperative day The 5 others were classified as having complicated cases because gastric retention persisted from 14 23 days or recurred after a temporary phase of adequate emptying If potassium loss were responsible for the impaired gastric function in the complicated group this should be demonstrable by comparing the mosaic of postoperative metabolism during the first 5 days in the complicated and uncomplicated groups Parenteral infusions supplied water and glucose electrolytes were not given until serum values showed clear changes

The cumulative losses of potassium and sodium during the first 5 days were essentially the same in both groups Toward the end of this period the serum potassium level fell slightly in some with complicated cases as did the serum chloride level with a rise in serum bicarbonate level but these changes followed increased fluid loss from the stomach Thus it appears that hypokalemia and hypochloremic alkalosis are the result not the cause of gastric atony and retention

Urinary excretion of sodium and potassium in the first 3 days in the two groups showed no differences As expressed by this function adrenal activity was the same in those with or without subsequent gastric retention

(1) A ta h sca dinav 112 317 3 5 1957

cium is depressed in acute pancreatitis and perforated ulcer are not clear but some common factor may be operative in both conditions

► [Since serum calcium levels may also drop precipitously in mesenteric infarction (New England J Med. 255 441 1956) the triad of abdominal catastrophes—acute pancreatitis perforated ulcer and mesenteric infarction—may present a similar front to confuse the diagnostician shock high serum amylase levels and hypoglycemia —Ed]

Role of Carbohydrates as Etiologic Agents Producing Dumping Syndromes Although it is generally accepted that hemodynamic disorders and phenomena mediated by the sympathetic and parasympathetic nervous systems characterize the dumping syndrome etiologic mechanisms responsible for these symptoms remain obscure A Dyk[9] (Kitzbuhel Austria) studied the role of various food substances in precipitating the syndrome

The syndrome never followed ingestion of pure protein solutions or fat emulsions symptoms occurred only if carbohydrates were given The interval between eating the carbohydrate and appearance of symptoms decreased progressively depending on whether high molecular compounds disaccharides or monosaccharides were given Equimolecular solutions of mineral salts caused diarrhea but no dumping symptoms thus ruling out pure osmolarity as a controlling factor in producing the syndrome

Dumping symptoms were elicited promptly when glucose (50 Gm in 150 Gm water) or galactose was given and somewhat less promptly but with equal intensity if mannose xylose or arabinose was used These sugars are effectively dextrorotatory Conversely if sugars effectively levorotatory were used such as fructose or levorotatory forms of the pentoses ribose and arabinose no symptoms developed

The dumping syndrome thus is precipitated by a chemically definable mechanism Since neither dextro nor levorotatory compounds can elicit dumping symptoms in a normal person it is postulated that intestinal enzymes normally convert dextro to levorotatory sugars but that this conversion is impaired in those susceptible to the dumping syndrome *Because of this impairment an abnormal product* directly responsible for the syndrome may accumulate

► [If the dumping syndrome still mysterious despite many proffered explanations really has such a specific pathogenesis it will be startling

(9) Wien klin. Wchnschr 5 1019 1021 D 28 1956

al cells of the small bowel were flattened mitotic activity had ceased and the mucosa was denuded with reduction in the height of the villi and depletion of stromal lymphocytes The treated group had similar symptoms but survived 4 11 days Infusions given for survival were followed by clinical improvement but copious diarrhea continued Leukocyte and platelet depletion was equal in both groups with almost complete absence after 4 days

Anorexia retching and vomiting on the day of irradiation were probably exaggerations of radiation sickness seen in man after therapeutic exposure The more severe symptoms on the second day may have been related to the morphologic changes in the gastrointestinal tract Terminal diarrhea was not accompanied by peristalsis and resembled that seen in paralytic ileus All symptoms at all stages of the reaction appeared to be aggravated by oral feeding Massive intestinal necrosis did not occur and epithelial regeneration was active after a week Morphologic intestinal changes therefore did not explain the gastrointestinal symptoms that continued into the 2d week after irradiation The manifestations of the hematologic syndrome to be expected at that period were in part controlled by antibiotics and administration of blood white blood cells and platelets

► [If man reacts like the dog the impact of this study is discouraging Even if the symptoms of the gastrointestinal syndrome are effectively combated with parenteral replacement therapy the late effects and the hematologic syndrome will inevitably be fatal —Ed.]

\Effective Antiemetic Agents were evaluated by John H Moyer[3] (Baylor Univ) as to pharmacologic rationale indications dosage and side effects (table) Although the action of antiemetic drugs is imperfectly understood they presumably block one or more of the afferent and efferent nervous mechanisms responsible for vomiting The vomiting center located in the brain stem does not initiate vomiting itself but is activated by stimuli arriving via different pathways One carries impulses from the chemoreceptor trigger zone situated in the floor of the 4th ventricle and sensitive to emetics such as apomorphine Vagal and sympathetic afferents carry stimuli from viscera to the vomiting center and other pathways transmit impulses from labyrinthine cerebellar and cortical areas

Thorazine® decreases the sensitivity of the chemoreceptor

(3) M Cl North Am 41 405-432 March 1957

Return of intestinal function was preceded by normalization of blood chemistry in only 2 of the 5 with complicated cases

► [Patients severely ill with gastrointestinal disorders and afflicted with vomiting or diarrhea often have low potassium levels in the blood It has therefore been assumed that the hypokalemia is responsible for the alimentary motor dysfunction especially if the patient improves after he is given some potassium Treatment however rarely consists of potassium solutions and nothing else The incrimination of hypokalemia and low tissue potassium stores as a specific and principal cause of gastrointestinal motor disorders is based on very little solid evidence and this report manifests healthy skepticism —Ed]

Experimental Therapy of Gastrointestinal Syndrome Produced by Lethal Doses of Ionizing Radiation Total body irradiation produces varying syndromes depending on dose and time after exposure The central nervous system syndrome is produced by massive exposure appears promptly and leads to death in a few hours The hemopoietic syndrome is produced by lethal doses with prolonged bone marrow depression causing death in the 2d week The gastrointestinal syndrome produced in dogs by superlethal doses is characterized by nausea vomiting and diarrhea presumably due to a direct effect on the alimentary tract and death in 3 5 days The predominant finding is epithelial damage to the small intestine with little impairment of absorption Death appears to be due to electrolyte and fluid depletion R A Conard E P Cronkite George Brecher and C P A Strome[2] (Nat l Naval Med Center Bethesda Md) studied the effect of extensive parenteral therapy on dogs exposed to superlethal radiation

Eight control dogs received 1 800 r ($LD_{50} = 375$ r and $LD_{100} = 600$ r) delivered by 2 Mev radiation Another 8 received 1 300-1 500 r Co^{60} radiation ($LD_{50} = 300$ r and $LD_{100} = 400$ r) Eleven receiving the same dose of Co^{60} were treated with antibiotics (600 000 units penicillin and 250 mg oxytetracycline or 150 mg streptomycin daily) parenteral fluids containing Na K Cl Mg PO_4 and lactate in 10% Travert® and 5% protein hydrolysate Plasma whole blood and white blood cell concentrates were given to some

Controls showed vomiting as the first symptom followed by mushy stools diarrhea bloody stools dehydration and death in 2 6-4 4 days At autopsy the serosa and mesentery were congested and the small intestine dilated The epitheli

(2) J Appl Phy ol 9 227 233 Septembe 1956

al cells of the small bowel were flattened mitotic activity had ceased and the mucosa was denuded with reduction in the height of the villi and depletion of stromal lymphocytes The treated group had similar symptoms but survived 4-11 days Infusions given for survival were followed by clinical improvement but copious diarrhea continued Leukocyte and platelet depletion was equal in both groups with almost complete absence after 4 days

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Thorazine® decreases the sensitivity of the chemoreceptor

(3) M Clin North America 41 405-432 March 1957

trigger zone and the irritability of the vomiting center It is thus useful in many vomiting states particularly in treatment of vomiting caused by drugs acting on the chemoreceptor center such as digitalis Its sedative effect makes it useful in treating alcohol induced vomiting Despite the fact that opiates irritate the chemoreceptor trigger zone Thorazine® is not too helpful in controlling nausea and vomiting pro-

RECOMMENDATIONS FOR ANTIEMETIC THERAPY

SOURCE OF EMESIS	RECOMMEND AGENT	DOSE (mg)	FREQUE CY†
Drug-Induced			
D gital	Thoraz	10-	q d
A t b t cs	Th azine	10-	q i.d
N trog must rd	Th ra e	25-50	q i.d.
Al h l states	Th r n	50-150	q d.
Op tes	B nam	25-50	b d.
	Ma o	50	t i d.
	D mamine	100	q i.d.
Inf ctions	Tho az	10- 5	q d
Toxicoses			
Diabet c ac do is	Th ine	10-2 ‡	q i.d
Uremia	Th ine	10-2	q i d
Carcin m tosis	Tho azin	10- ‡	q i.d.
Radiation si kness	Th a	10-.5‡	q i d.
Other	Thorazin	10-2 ‡	q i.d.
Postoperat V miting			
Prophyla t	D am mine	50	t d-q i.d.
	B nadryl	50-100	t d.-q i.d.
	M in	50	t.i.d
Therapeutic	Tho az e	-5-50§	t.i.d.
P egnancy	Bonamine (with without pyri d xine)	25-50	h.s.
Motion Sickness			
Air sickness	Sc polamine o	0 65-1 0	
	Bonamine	2	b i.d.
Seas kness	Bo min	50	q d.

Refers t o al dose p nteral d es e u ually sl ghtly less
†Freq e cy q d on /day b i d tw ce/day t. d 3 times/day q d., 4 tim /day h bedt me
‡M y ea e d e to 50 mg f ec ary to est m t g
§F t dose usually admin te ed p nter lly

duced by opium derivatives An initial intramuscular dose of 25 mg is usually necessary to treat vomiting intravenous Thorazine® is rarely used as severe hypotension and tachycardia may develop Deep intramuscular injection may be painful and irrespective of route of administration about 12% of patients show hypotension In psychiatric patients receiving large doses of Thorazine® incidence of jaundice is about 1 4% Agranulocytosis may develop w [illegible] weeks

after Thorazıne® therapy ıs begun Because of these sıde ef fects ıt ıs usually preferable to use other agents ın treatıng moderate nausea and vomıtıng or ın preventıng these symp toms

Dramamıne® Bonamıne and Marezıne® exert antıcho lınergıc actıvıty and depress vestıbular sensıtıvıty Possıbly because of these actıons they are useful to treat opıate ınduced vomıtıng and motıon sıckness Dramamıne® and Benadryl® whıch ıs sımılar and equally effectıve are useful for prophylaxıs of postoperatıve vomıtıng Bonamıne and Marezıne® less so Once postoperatıve vomıtıng occurs Thorazıne® ıs necessary

Bonamıne ıs partıcularly useful ın treatıng nausea and vomıtıng of pregnancy Thorazıne® ıs equally useful but ıs a second choıce because of ıts sıde effects Dramamıne® has lıttle to offer Compazıne shows promıse and appears more potent than Thorazıne® and ıs less hypotensıve

For motıon sıckness Bonamıne and Dramamıne® are the agents of choıce Scopolamıne though effectıve produces untoward sıde effects and Thorazıne® ıs relatıvely ıneffec tıve In condıtıons such as vomıtıng assocıated wıth antı bıotıc admınıstratıon Benadryl® Dramamıne® Bonamıne and Bonadoxın® (Bonamıne plus pyrıdoxıne) may be trıed first Thorazıne® ıs ındıcated ıf these agents prove ıneffec tıve Almost any of these agents may cause sedatıon dızzı ness dry mouth weakness fatıgabılıty blurrıng of vısıon lıghtheadedness and occasıonally headaches and ınsomnıa

► [The physıcıan dealıng with gastroıntestınal problems ıs possıbly more fearful of the ıcterogenıc effects of Thorazıne® than ıs the author Not only ıs Thora ne® hepatıtıs a problem ın ıtself (see page 572) but the possıbılıty of Thorazıne® hepatıtıs has made the dıfferentıal dıagnosıs of jaundıce even more dıfficult If one sees a jaundıced patıent who was gıven Thorazıne® for some preıcterıc symptoms ıs the ensuıng jaundıce an ex pressıon of the treatment or of an underlyıng bılıary or hepatıc process responsıble for the symptoms that antedated the onset of jaundıce?—Ed.]

Investıgatıon of Nonulcer Dyspepsıa by Gastrıc Bıopsy A Wynn Wıllıams Felıcıty Edwards T H C Lewıs and N F Coghıll[4] define nonulcer dyspepsıa as a condıtıon ın whıch abdomınal or thoracıc symptoms other than dys phagıa occur ın relatıon to eatıng and no anemıa or organıc cardıac renal or gastroıntestınal dısease ıs demonstrable Of 775 new outpatıents seen durıng 1952 55 468 (60 4%) could be so classıfied

(4) B ı M J 1 372 377 F b 16 1957

Of 200 suction biopsies of the body of the stomach 45% were normal 36% showed miscellaneous minor mucosal change (epithelial abnormalities and/or increased inflammatory cells in the stroma), 14 5% had chronic atrophic gastritis (glandular atrophy with infiltration of the stroma with inflammatory cells) and 4 5% had chronic superficial gastritis (same as atrophic except glandular atrophy was superficial) Thus more than half the patients had gastritis but only 19% had major abnormalities Gastric mucosal changes were more common in older patients chiefly because of increased *incidence of chronic atrophic gastritis*

In 185 patients multiple biopsies taken at one time showed that a single biopsy was representative in all but 10 15% of cases Patchy distribution of gastritis may have accounted for those in whom a single sample was not representative Among 26 patients examined serially unexplained differences in the serial samples were found in 38 5% a high figure

Histamine stimulated gastric secretion was measured in 76 5% of the patients Compared with the group with normal gastric mucosa those with miscellaneous minor changes failed to secrete HCl 6 times as often and those with superficial and atrophic gastritis 15 times as often This argues against the possibility that the miscellaneous minor changes are within normal limits and have no significance On the other hand the relation of the gastric changes to the symptoms of the patients is a difficult problem and no conclusions on this relation are drawn

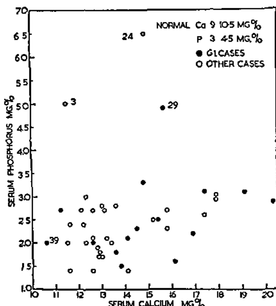
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Gastrointestinal Symptoms as Clue to Diagnosis of Primary Hyperparathyroidism Review of 45 Cases by Walter T St Goar[5] (Columbia Univ) showed that 16 (36%) had clinically significant gastrointestinal symptoms with abdominal pain prominent in 9 The symptoms are summarized in the table Peptic ulcers were demonstrable in 4 (8 8%) who had typical ulcer pain These symptoms in themselves are meaningless but may lead to correct diagnosis particularly if accompanied by others suggestive of hyperparathy

(5) Ann. I t. Med 46 102 118 J uary 1957

roidism such as minimal urinary or skeletal symptoms or lassitude of body and mind often erroneously diagnosed as psychoneurosis

Gastrointestinal symptoms subsided promptly after para thyroidectomy in 11 of the 16 and the 9 with abdominal pain were all relieved One had postoperative nausea and vomit ing which subsided before discharge 1 died before operation



F g 84—P p t rum org d ph ph l ls (Courte y of St. Goa W T Ann I t M d 46 10 118 J n ry 1957)

was performed and 3 continued to have gastrointestinal symptoms postoperatively

The mechanism by which hyperparathyroidism gives rise to abdominal pain is not clear Hypercalcemia which ac counts for most clinical manifestations of hyperparathyroid ism is probably responsible though serum calcium and phos phorus values in hyperparathyroid patients with and with out digestive symptoms had the same distribution (Fig 84) In sympathetic ganglions increased calcium ion con

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4 in the jejunum In 19 patients the islet cell tumor was malignant 7 of the 19 patients had multiple tumors and in 11 there were metastases beyond the pancreas Two patients had mixed tumors containing beta cells associated with hypoglycemia Of the 5 patients with benign adenomas 3 had multiple tumors Tumors of other endocrine glands were found in 5 patients a pituitary basophil adenoma a pituitary eosinophil adenoma with acromegaly and parathyroid adenoma an adrenal cortical adenoma and 2 multiple adenomas involving the pituitary parathyroid and adrenal cortex.

Of the 24 patients 18 were operated on for ulcer and 4 for tumor In 50% of the patients operated on for ulcer the pancreatic tumor was not recognized until autopsy These 9 patients had 23 operations for 9 primary and 26 recurrent ulcerations and all died of ulcer complications Of the 11 patients in whom it was recognized that peptic ulceration was associated with a pancreatic tumor 6 died 3 died of ulcer soon after operation and at autopsy an overlooked pancreatic tumor was found in the other 3 metastatic tumors were found at autopsy but despite this average survival time was 6 6 years

A humoral agent produced by these pancreatic tumors is suggested as the cause of these recurrent ulcers because (1) gastric hypersecretion was not controlled by interrupting cephalic and antral stimuli but was eliminated by removal of the pancreatic adenoma and (2) only patient in whom the pancreatic adenomas were completely excised recovered from the invariably fatal ulcer disease It would seem advisable to examine the pancreas of patients operated on for peptic ulcer especially if the primary ulcer is atypically located or is a recurrent marginal ulcer The surgical attack should include removal of the tumor and a standard ulcer operation Since small adenomas are difficult to locate resection of the body and tail of the pancreas should be considered as an alternate for total gastrectomy in control of intractable recurrent ulcers

The entity described is not only fascinating in itself but should shed further light on the pathogenesis of peptic ulceration These patients are tremendous hypersecretors In one case (R. M Donaldson P Von Eigen and R Dwight—personal communication) constant gastric aspiration yielded a 24 hour volume of 11 700 cc. How endocrine tumors and this voluminous gastric activity are related is not clear The concept that excess glucagon secretion by the islet cell tumors might be responsible has apparently not been substantiated. Furthermore it is apparent that many

SYMPTOMS

General	G I Cases (%)	All Cases (%)
Weakness easy fatigability	50	31
Weight loss (over 10 lb in last yr)	25	11
Gastrointestinal		
Constipation	31	29
Nausea and/or vomiting	56	20
Marked anorexia	25	16
Epigastric pain	38	13
Diffuse abdominal pain	13	4
Diarrhea	0	4
RUQ postprandial distress	6	2

centration impedes transmission of afferent stimuli and diminishes efferent discharges in presence of a constant amount of perfusing acetylcholine This effect plus that of hypercalcemia on reducing neuromuscular excitability presumably leads to decreased tone of the gastrointestinal tract

► [Although the association of gastrointestinal symptoms with hyperparathyroidism is deservedly emphasized as a clinical fact a good explanation for this association is still wanting One would not usually consider decreased tone an adequate explanation of the type of gastrointestinal complaints mentioned. In particular decreased gastrointestinal activity would not explain the high incidence of peptic ulcer in patients with hyperparathyroidism According to a recent brief survey (Lancet 1 341 Feb 12 1955) this incidence was 15 14 and 9% respectively in 3 different series

As is evident from the subsequent abstract peptic ulceration of the gastrointestinal tract may be common not only in hyperparathyroidism but in association with a variety of tumors of endocrine organs —Ed.]

Ulcerogenic Tumor of Pancreas Edwin H Ellison[6] reviewed clinical and autopsy records of the Ohio State University Medical Center for the past 10 years and found 5 cases of ulcerogenic tumors of the pancreas bringing the total of reported cases to 24 This new clinical entity consists of a noninsulin producing islet cell tumor associated with *fulminant peptic ulceration*

All patients for whom sufficient data were available for evaluation had gastric hypersecretion Of 7 in whom 12 hour night gastric secretion was measured 6 secreted more than 1 000 cc 4 more than 2 000 and 1 3 170 cc In 6 total free hydrochloric acid in the 12 hour night secretion ranged from 66 to 308 mEq and exceeded 100 mEq in all but 2 Of the 24 patients 5 had multiple ulcers Of the 30 ulcers in these patients 1 was in the esophagus 4 in the stomach 13 in the first part of the duodenum 6 in the second 3 in the third and

(6) Surgery 40 147 170 July 1956.

4 in the jejunum In 19 patients the islet cell tumor was malignant 7 of the 19 patients had multiple tumors and in 11 there were metastases beyond the pancreas Two patients had mixed tumors containing beta cells associated with hypoglycemia Of the 5 patients with benign adenomas 3 had multiple tumors Tumors of other endocrine glands were found in 5 patients a pituitary basophil adenoma a pituitary eosinophil adenoma with acromegaly and parathyroid adenoma an adrenal cortical adenoma and 2 multiple adenomas involving the pituitary parathyroid and adrenal cortex

Of the 24 patients 18 were operated on for ulcer and 4 for tumor In 50% of the patients operated on for ulcer the pancreatic tumor was not recognized until autopsy These 9 patients had 23 operations for 9 primary and 26 recurrent ulcerations and all died of ulcer complications Of the 11 patients in whom it was recognized that peptic ulceration was associated with a pancreatic tumor 6 died 3 died of ulcer soon after operation and at autopsy an overlooked pancreatic tumor was found in the other 3 metastatic tumors were found at autopsy but despite this average survival time was 6 6 years

A humoral agent produced by these pancreatic tumors is suggested as the cause of these recurrent ulcers because (1) gastric hypersecretion was not controlled by interrupting cephalic and antral stimuli but was eliminated by removal of the pancreatic adenoma and (2) only patients in whom the pancreatic adenomas were completely excised recovered from the invariably fatal ulcer disease It would seem advisable to examine the pancreas of patients operated on for peptic ulcer especially if the primary ulcer is atypically located or is a recurrent marginal ulcer The surgical attack should include removal of the tumor and a standard ulcer operation Since small adenomas are difficult to locate resection of the body and tail of the pancreas should be considered as an alternate for total gastrectomy in control of intractable recurrent ulcers

The entity described is not only fascinating in itself but should shed further light on the pathogenesis of peptic ulceration. These patients are tremendous hypersecretors In one case (R. M Donaldson P Von Eigen and R Dwight—personal communication) constant gastric aspiration yielded a 24 hour volume of 11 700 cc. How endocrine tumors and this voluminous gastric activity are related is not clear The concept that excess glucagon secretion by the islet cell tumors might be responsible has apparently not been substantiated Furthermore it is apparent that many

of the patients suffer not only from islet cell tumors but from multiple glandular adenomas Three of 8 patients with such lesions involving the the pituitary parathyroids and pancreatic islets had peptic ulcer (J Clin Endocrinol 13 20 1953) and reading of the actual case reports cited by Ellison would suggest that more than 5 patients had endocrine adenomas in addition to those found in the pancreas —Ed]

Primary Nonspecific Ulcers of Small Intestine Clinicopathologic Study of 18 Cases with Follow up of 14 Previously Reported Cases is presented by Carl G Morlock Homer R Goehrs and Malcolm B Dockerty[7] (Mayo Clinic and Found) The 18 patients seen since 1945 were aged 11 71 though most were middle aged 13 were males Early signs and symptoms of the ulcers were so mild and indefinite that medical advice was rarely sought before onset of hemor



Fig 85 —Sharply defin d ol t y t llate ulc f l m w th ma ked assoc ted n ow g f bow l lumen Th cke ng nd dema th t har t ri l on f e g o l nte t s a e absent (Cou t y of M lo k C G t al G tr e te logy 31 667 680 Dec mb 1956)

rhage obstruction or localized perforation the 3 common complications reported Sixteen patients had recurring episodes of crampy midabdominal pain suggesting partial obstruction of the small bowel Hematemesis melena anemia or a combination of these findings pointed to gastrointestinal bleeding in 5 In 3 symptoms were somewhat suggestive of duodenal ulcer Diarrhea though mentioned by half the patients was mild

Physical signs were usually those of a complicating intestinal obstruction Four had no notable abdominal findings and no well defined abdominal masses were palpated A thin barium suspension given to 9 revealed no x ray evidence of small bowel disease in 3 and delineated the level of an obstructing lesion in 6 In 4 a short stenosed segment of gut

(7) Ga troe t ology 31 667-680 Decembe 1956

was seen suggesting inflammatory obstruction but as a niche was never identified the diagnosis of ulcer of the small intestine was not made radiologically

All patients were treated by resection of the segment containing the ulcer with an operative mortality of 11% The ulcers were ileal in 12 and jejunal in 6 In 3 more than one ulcer was present The ulcers were well defined and resembled peptic ulcers of the stomach and duodenum (Fig 85) Peritoneal reactions associated with ulcers included 3 localized abscesses with sinus tracts 3 with nonsuppurative thickening of the mesentery and 5 with localized peritonitis There was no instance of free perforation

Of the 9 living patients from the previously reported series of 14 with nonspecific ulcers of the small bowel 6 had been essentially well and 3 had had bleeding or definite recurrence of the disease Nine of the present series of 18 were followed for 1½ 6 years 8 were well and 1 had multiple jejunal ulcers and a bleeding duodenal ulcer

No cause for the ulcers was found Obvious mechanical traumatic vascular or infectious factors could not be incriminated and careful search ruled out existence of gastric heterotopia which might lead to peptic digestion Analysis of the postoperative course however emphasized that the insult leading to the development of these solitary ulcers is rarely repeated

► [The figures cited do not quite seem to justify the sanguine prognosis given to patients with nonspecific ulcers of the small bowel—except possibly in the etymologic sense of sanguine In view of the 2 preceding abstracts one might almost predict that some of the patients must have had endocrine adenomas —Ed]

Mucosal Pattern of Mesenteric Small Intestine Anatomic Study Robert D Sloan[8] (Johns Hopkins Univ) correlated the anatomic and radiologic appearance of the adult human small bowel Well preserved autopsy specimens from the proximal jejunum and distal ileum were studied under various degrees of natural and artificial distention With increasing distention jejunal segments increased in both diameter and length and the straightening of the multiple convoluted mucosal folds produced corresponding changes in the radiologic pattern (Figs 86 and 87) Ileal loops when contracted displayed a prominent mucosal pattern but on distention the walls thinned out and mucosal folds

(8) Am J Roentgen 1. 77 651 669 Ap 1, 1957

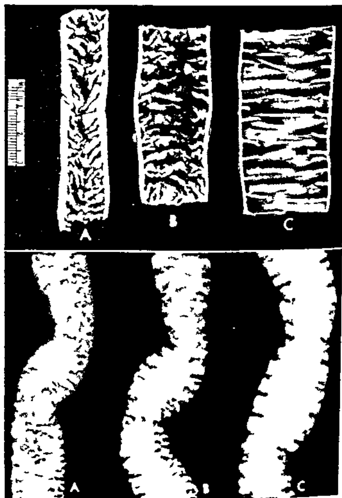


Fig. 86 (top).—Jejunal mucosal pattern obtained with artificial distention of initially contracted segment. *A* represents initially contracted state and *B* and *C* progressive degrees of distention of immediately adjacent segment.

Fig. 87 (bottom).—Specimen x-rays showing changes in appearance of folds associated with artificial distention. *A* represents pattern obtained with small amount of barium suspension outlining tortuous primary and secondary folds. *B* and *C* represent same loops distended more fully with barium suspension.

(Courtesy of Sloan, R. D.: Am. J. Roentgenol. 77:651-669, April 1957.)

were low infrequent and irregularly spaced The radiologic appearance under such conditions resembled that seen when ileal loops are filled in retrograde fashion during a barium enema

The size of the mucosal folds of contracted jejunal and ileal segments varied considerably from one case to another Spontaneous abrupt changes in degree of contraction and mucosal pattern were frequently observed especially in the ileum (Fig 88) Although longitudinal distribution of mu

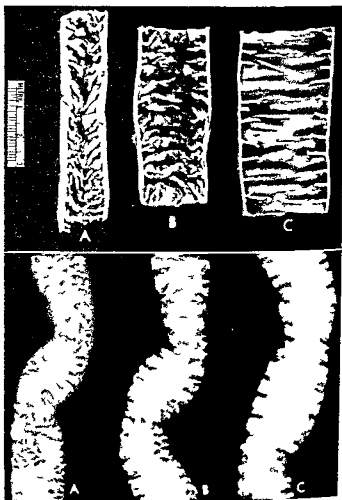


Fig 88 —Closely adjacent ileal loops showing f ly marked variations d gre f d tention commonly found at t psy Associat d h ge in mu sal patterns shown in the specimens f om diffe ent aut p ies (Courtesy of Sloan R. D Am J Roentgenol. 77 651 669 April, 1957)

cosal folds seen during peristaltic activity when the living intestine is studied radiologically could not be found or reproduced in autopsy specimens the mucosal pattern of the small bowel usually appears to reflect the state of contraction of the intestinal wall as a whole rather than an isolated effect of the muscularis mucosae

Intermittent Arteriomesenteric Occlusion of Duodenum. According to Lowell S Goin and Stefan P Wilk[9] (Univ of California Los Angeles) duodenal stasis may be divided into (1) chronic organic obstruction caused by neoplasm bands or congenital defects and (2) intermittent mechanical

(9) Radiology 67 729 737 November 1956



F g 86 (top) —J ; n l mu osal p tt rn bt ed w th art fic al d tent f ın t ally nt t d gm t *A* p e t ı t l t a t d st t a d *B* d *C* prog es d g of d te t on f mmed tely adȷ t s gme t

F g 87 (bottom) —Sp m x ay h w g b g app a e f f ld a so c t d w th rt fic l d t t on *A* p t p tt n obt d w th m ll am t of bar m pen ıon tl g t tu p m y a d o da y f ld *B* d *C* rep sent same loop dist d d m f lly w th b um susp o

(Courte y of Sl n R D Am J Roentge ol 77 651 669 Ap 1 1957)

described) and 1 successfully by postural exercises the 6th had colonic cancer also

Arteriomesenteric occlusion of the duodenum is neither common nor extremely rare Incidence was roughly 1/500 patients in whom upper gastrointestinal series were performed Clinicians and radiologists should be more aware of the condition and recognize it more often

► [A rash of articles on this condition has appeared in the recent year (Acta radiol 45 441 1956 A M A Arch Surg 73 296 1956 Schweiz Med Wchnschr 87 230 1957) all emphasizing the point that the medical profession is insufficiently aware of arteriomesenteric occlusion of the duodenum As far as I am concerned I hope they remain unaware *not* of the syndrome and its radiologic manifestations but of the alleged explanation Moderate dilatation to marked ileus of the duodenum with churning motor activity is found in many conditions of malnutrition particularly those that are psychogenic and chronic It is thus a characteristic finding in anorexia nervosa The sequence of events however is that duodenal tone and motility are impaired first presumably as a result of malnutrition emotional turmoil or both Then and only then normal structures such as the spine and the mesenteric root may offer a relative obstruction. If the malnutrition is overcome duodenal tone returns to normal and the apparent obstruction disappears Conversely if surgery is attempted the long term results are frequently disappointing for the motor abnormality is not apt to be confined strictly to the duodenum — Ed]

Regional Ileitis Complicating Pregnancy The records of 84 pregnancies in 53 patients with regional ileitis culled from over 600 cases followed for 27 years were reviewed by Burrill B Crohn Harry Yarnis and Burton I Korelitz[1] (Mount Sinai Hosp New York) There were 133 married women in the 600 48 of whom had had 88 pregnancies before and unrelated to the ileitis

In 34 patients (45 pregnancies) ileitis was inactive at onset of pregnancy This group had had 7 normal pregnancies and 1 miscarriage before ileitis In 28 (62%) the disease remained inactive during pregnancy and post partum 7 recurrences during pregnancy and 10 post partum comprised a recurrence rate of 38% In 36 of the 45 pregnancies deliveries were normal the others showed various obstetric catastrophies These figures compared well with those of a normal population group Breakdown of the group into those with (19) and without (15) prior definitive surgery revealed 22 of 27 pregnancies (81%) without recurrence in the first group but only 5 of 18 pregnancies (28%) without flare up of ileitis in the patients not operated on

(1) G t oenter l gy 31 615-628 Dec mbe 1956

obstruction due to compression of the third portion of the duodenum between the spine and the mesenteric root bearing the superior mesenteric artery Such occlusion occurs most commonly in the lean asthenic female and is aggravated by loss of weight worry and relaxation of the abdominal walls Symptoms such as upper abdominal fulness and cramps occur intermittently Diagnosis is made by x ray

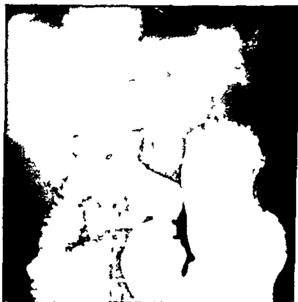


Fig 89—Marked d l tat on of p x mal duodenum with compl t d truction at le el f t n erse po t on (C rtesy of Goin L. S a d Wilk S P Rad ol gy 67 729 737 November 1956)

which shows dilatation of the proximal duodenum with an abrupt obstruction of the duodenal lumen as it crosses the spine (Fig 89) Normal mucosa is often demonstrable The obstruction is aggravated when the patient is standing relieved when he lies prone Back and forth movement of the opaque medium in the dilated descending duodenum is characteristic

Of 6 patients studied 2 were treated successfully by duodenojejunostomy (1 2 year follow up) 1 unsuccessfully by gastroenterostomy 1 by partial gastrectomy (results not



Fig 90 —Barium study in case of incomplete mesenteric f rction how g nar ow d segment n distal i i m w th ffacement f m os d ou l t a t on to dilated bow l proximally and d tally (Courtesy f W lf B S and Ma hak R. H Rad ology 66 701 707 M y 1956)



Fig 91 —Same se. Tubula fibrotic segment 7 cm. long with con cal t an tion to djacent bow l (Co rtesy of Wolf B S d M rshak R. H Rad logy 66 701 707 M y 1956)

lar irregularity or overhanging edges are not seen Transi tion to dilated bowel proximally and normal bowel distally is smooth concentric and fairly abrupt

CASE 1 —Woman 54 had an incarcerated loop of ileum in a right femoral hernia At operation the loop appeared viable and was not excised Three weeks later symptoms of intestinal obstruc tion appeared and a barium meal revealed a segment of tubular stenosis in the ileum On re-exploration a segment of fibrotic nar rowed ileum was resected Recovery was uneventful

CASE 2 —Man 40 had signs of intestinal obstruction One year

Thirty pregnancies took place in 23 patients with active ileitis Disease subsided during pregnancy in 14 (with post partum recurrence in 10) was unchanged in 12 (postpartum exacerbation in 2) and aggravated in 4 (postpartum subsidence in 3) One of the 4 showing aggravation required cesarean section in the 5th month 2 had normal pregnancies and 1 an eight months delivery Twenty six (87%) of the 30 pregnancies resulted in full term deliveries

There were 3 patients with onset of ileitis during pregnancy with no full term pregnancies The course of the disease was severe in all 3 and 1 died Six other patients had ileitis which began post partum Four are well 1 having required surgery and 2 have mild recurrences Five had completed full term deliveries 1 had a miscarriage in the 6th month

Regional ileitis is no bar to fecundity and successful pregnancy is possible in most patients Although less deleterious than in ulcerative colitis pregnancy in ileitis tends to exert an unfavorable effect particularly if the disease is active at time of conception Ileitis appearing for the first time during pregnancy may be very severe Patients with inactive ileitis who have had surgery for the disease tend to survive pregnancy without difficulty

Segmental Infarction of Small Bowel is described by Bernard S Wolf and Richard H Marshak[2] (Mount Sinai Hosp New York) in four cases Vascular occlusion in the intestinal tract usually constitutes a surgical emergency In a few patients however *short segments of bowel* undergo partial devitalization rather than gangrene of the entire wall with perforation In this event healing may take place but extensive mucosal destruction and persistent ischemia preclude restitution to a normal state Inflammatory granulation tissue forms with subsequent fibrosis and stricture formation Dilatation of proximal bowel occurs terminating abruptly in a narrowed firm tubular structure 2 5 in long and one half to one fourth the diameter of normal bowel The mesentery of the involved segments is thickened and fibrotic and contains hyperplastic lymph nodes

Roentgen findings in segmental infarction consist of tubular narrowing of a segment usually 3 in long with effacement of the mucosal pattern but mucosal destruction nodu

(2) Rad 1 gy 66 701 707 M y 1956

expired CO_2 and blood were collected for estimation of radio activity and chylomicron counts were done on the plasma

The amounts of lipid absorbed were expressed as mg /sq dm body surface The rates calculated from direct estimation of residual intestinal radioactivity were from 1 5 to 3 5 times greater than those calculated by the direct chemical recovery method Thus it would appear that these two methods meas ure different phenomena or that one is inaccurate The slower rate of absorption yielded by the generally accepted chemical recovery method might be explained by selective absorption of free labeled fatty acid or by secretion of lipid into the alimentary tract with consequent dilution of the recovered radioactive lipid The latter interpretation appears reasonable since specific activity of recovered lipid was less than that of fed fat If lipid secretion occurs it may be calcu lated that the amounts secreted in these animals varied from 20 to 47% of the amount fed

The results of the indirect methods did not agree closely with those of either of the direct methods but were more in accord with the absorption values based on radioactivity The radioactivity in the blood and in expired CO_2 were in good agreement with the chylomicron counts These results suggested a direct relation between the indirect methods and indicated that all three reflected lipid absorption despite the fact that different phenomena were being measured The in direct methods should be useful as a relative measure of the rate of fat absorption

► [This and the succeeding three abstracts indicate the increasing interest in the measurement of absorption The basic study by Tidwell and his associates emphasizes the difference between the direct and indirect meth ods as well as the fact frequently ignored that the fecal output of a cer tain substance does not provide a measure of the unabsorbed fraction of the amount ingested Other factors affecting fecal output are endogenous secretion and contributions made by bacterial life See also page 545 — Ed]

I^{131} Labeled Fat in Study of Intestinal Absorption Julian M Ruffin William W Shingleton George J Baylin Jacqueline C Hymans Joseph K Isley Aaron P Sanders and M Frank Sohmer Jr[4] (Duke Univ) measured fat absorp tion in 180 patient by means of I^{131} labeled fat

METHOD —Two fat emulsions were prepared (1) 200 ml peanut oil was emulsified with 200 ml water and 15 ml Tween* 80 (2) 45 ml peanut oil and 5 ml I^{131} labeled glycerol trioleate (2 mc

(4) New England J Med 2 394 397 September 7 19 6

earlier two gangrenous toes had been amputated Bowel obstruction abated spontaneously and an 18 cm necrotic cast of small intestinal wall was passed in the stool Roentgen examination 2 weeks later revealed a segment of tubular stenosis in the midjejunum with moderate proximal dilatation Intestinal obstruction recurred 4 weeks later and required operation A narrowed segment of bowel matted intestinal loops and purulent exudate were found. The segment was removed but partial intestinal obstruction continued Repeat barium study revealed a 2 cm area of marked stenosis in the ileum This was resected and the patient gradually recovered Obliterating endophlebitis of the mesenteric veins was the significant finding in the operative specimen

CASE 3—Man 61 had left upper quadrant crampy abdominal pain for 12 days Barium study revealed distal jejunal irritability and spasm After 3 weeks partial intestinal obstruction developed and repeat barium study uncovered tubular narrowing in the distal jejunum (Fig 90) The jejunal segment was resected and was described as showing fibrosis with chronic nonspecific inflammation and stenosis presumably due to previous ischemic necrosis (Fig 91)

CASE 4—Man 50 had low abdominal pain distention and vomiting for 5 weeks He had marked tenderness in the left upper quadrant X rays revealed a 4 cm segment of narrowed jejunum which on resection exhibited pathologic changes grossly and microscopically similar to those in Case 3

Symptoms in all cases were those of small intestine obstruction In the first two a definite cause for segmental vascular impairment could be identified Although in the latter pair the exact etiology was unknown since x ray and pathologic findings were similar to the others the underlying cause was assumed to be thrombotic or embolic mesenteric occlusion

Measurement of Rate of Fat Absorption is done either directly by determination of residual lipid in the alimentary tract after a fat meal or indirectly by serial estimations of fat in the plasma after such feeding Herbert C Tidwell Carolyn Dunkelberg William A Wood and William W Burr Jr[3] (Southwestern Med School) point out that both direct and indirect methods are influenced by factors other than the actual absorption of fat Five methods for estimating the rate of fat absorption were compared

Rats prepared with a fat free fluid diet for 48 hours received by intragastric tube 0 3 ml of 1 3% C^{14} labeled palmitic acid in olive oil/sq dm body surface Hourly samples of

(3) J B 1 Chem 220 733 740 June 1956

► [One reason for the increased interest in the study of absorption is the availability and relative simplicity of methods using radioactively tagged compounds The impressiveness and newness of isotopic work however leads some readers to believe that the mere use of these agents permits new discovery and better diagnosis This is not necessarily the case. The use of an isotopically labeled protein or fat may make an absorption test easier to perform but will not, per se make it more accurate or discriminative than a comparable biochemical test. Tests such as described in the preceding and succeeding abstracts for example do not differentiate between malabsorption caused by pancreatic disease and a small bowel disorder such as sprue Furthermore as the next abstract shows radioactively labeled substances are no more sensitive in detecting mild to moderate impairment of absorption (in this case caused by pancreatic disease) than are biochemical methods —Ed.]

Use of I^{131} Labeled Albumin in Diagnosis of Pancreatic Disease Pancreatic digestion was studied by Robert J Freeark Donald D Kozoll and Karl A Meyer[5] (Cook County Hosp) by measuring the radioactivity appearing in the blood at hourly intervals after ingestion of a meal of pure gelatin (0 5 Gm /kg) with 100 μc I^{131} labeled human serum albumin administered after a 12 hour fast and 72 hours of thyroid blockage with Lugol s solution Whole blood volume was measured by dilution technics or assumed to be 80 cc /kg Results were expressed as percentage of ingested isotope in the whole blood volume at a given hourly interval

The peak level in normal persons was never under 10% of ingested isotope and occurred in 2 3 hours Patients with nonpancreatic diarrhea (regional ileitis amebiasis acute nonspecific gastroenteritis and nontropical sprue) were at the lower limits of normal but peak concentration never fell under 10% Four with moderate pyloric obstruction reached peak concentrations more slowly than controls but levels always rose over 10% within the first 4 hours

Nine patients with pancreatic insufficiency showed flatter curves with peak levels over 5% in 1 in the other 8 the level remained under 4% Diarrhea was not constant in all but repetition of the test during diarrhea free periods yielded similar results

Six of 8 patients with obstructive jaundice due to carcinoma of the head of the pancreas showed definite pancreatic insufficiency by the test A flat test curve in obstructive jaundice thus indicates both pancreatic and common duct obstruction and suggests pancreatic carcinoma Only 1 of 22 with nonpancreatic obstructive jaundice had evidence of abnormal protein digestion In this patient a stone was im

(5) S g ry 41 268 275 F bruary 1957

I^{131}) were emulsified with 50 ml water and 4 ml Tween® 80 Fasting patients drank a mixture of the two emulsions (1 mg/kg) prepared so the total dose contained 25 mc I^{131} Twenty drops of *Lugol s solution* was taken after the test meal Venous blood (2 ml) was drawn at hourly intervals for 6 hours Total blood content of I^{131} was calculated from the radioactivity of the sample and the blood volume (assumed to be 7 2% of body weight) All stools passed within 48 hours of the test meal were collected and counted directly in their containers and radioactivity was expressed as percentage of ingested dose Normal values were determined in 33

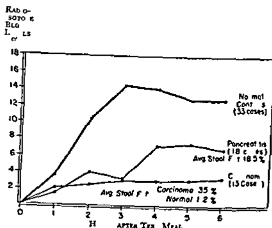


Fig 92—Rad o otope blood levels (average curves) in d se ses of pa as (ch n c pa c t t and carc noma) (Courtesy of Ruffin J M et al New E g la d J Med 255 594 597 Sept. 27 1956)

control subjects (Fig 92) Stool radioactivity greater than 5% of the ingested dose was considered abnormal

The average curve for radioisotope blood levels and average isotope content of stools were within normal limits in 44 patients with functional gastrointestinal disorders 4 with sprue in remission 8 with cirrhosis and 8 with ulcerative colitis However the average blood level of isotope was decreased and fecal I^{131} elevated in 1 sprue patient in relapse 18 with chronic relapsing pancreatitis 13 with carcinoma of the pancreas 2 with Whipple s disease 3 with regional enteritis 64 with partial gastrectomy and 15 with vagotomy and gastroenterostomy When single tests were analyzed however normal blood and stool radioactivity was found in 5 of the 18 patients with chronic pancreatitis 37 of 79 with surgery for peptic ulcer and 1 with carcinoma of the body and tail of the pancreas

the dose recovered within 24 hours 55% was recovered after fatty acid In both cases only 2-4% of the dose remained in the blood 24 hours after the test meal No explanation was apparent for the appearance of radioactivity earlier and in greater concentration in serum and urine after olive oil than after oleic acid

In patients with enzyme deficiency the normal response was reversed serum concentrations of radioactivity were higher after fatty acid ingestion than after fat

► [It was emphasized above that the use of isotopically labeled substances does not, by itself endow an absorption test with any unusual qualities On the other hand tests may be designed so that advantage is taken of the isotopic label to yield information not available otherwise The preceding and following abstracts are examples of use of such technics Others (Clin Chem 2 274 19 6 Proc Soc Exper Biol & Med 94 807 1957) are also comparing the absorption of a radioactively labeled whole food with the absorption of one of its products of digestion similarly labeled to differentiate between malabsorption caused by pancreatic insufficiency and by small intestinal disease This is apparently not only theoretically promising but works in practice It must be remembered however that products of digestion if introduced into the small gut in any quantity are irritant osmotically and chemically a fact which may affect the absorption curve

The next abstract illustrates one of the available technics whereby a radioactively labeled substance is used to separate fecal material of endogenous and exogenous origin —Ed]

Metabolic Study Following Oral Calcium[4] Administration in Patient with Nontropical Sprue is reported by Sidney Fink and Daniel Laszlo[7] (Montefiore Hosp New York)

Man 45 with history of duodenal ulcer and thromboangiitis obliterans and intermittent diarrhea was hospitalized in an exacerbation characterized by shock watery diarrhea and tetany Hemoglobin value was 9 Gm /100 ml and serum levels were potassium 2 9 mEq/L calcium 5.2 mg and albumin 2 9 Gm /100 ml Prothrombin time was 30 seconds with a control of 11 seconds An oral glucose tolerance test showed a flat curve There was excessive fecal fat After improvement achieved by cortisone and supportive measures he was studied for 10 metabolic periods of 6 days each During the entire study vitamins A and D were given each day intramuscularly and 50 75 mg cortisone/day was given for the first half of the study

Dietary intake of about 200 mg calcium/day was supplemented by 11 Gm calcium gluconate (953 mg calcium) and on the first day of the study a single oral dose of Ca[4] was given During the 30 days of cortisone therapy and well being urinary calcium excretion was low (6-28 mg /24 hours) fecal excretion was high (average values 414 710 mg /24 hours) calcium balances were positive throughout (average +515 mg /24 hours) and serum calcium level

(7) G t oent logy 3 689 703 April 1 57

pacted at the ampulla of Vater possibly obstructing the pancreatic ducts and the common duct Three of the jaundiced patients with normal absorption of I^{131} labeled albumin had carcinoma of the ampulla of Vater The postulated explanation for normal digestion in these patients was that the tumor originated in the common duct and a separate pancreatic duct carried the secretions into the intestine

Six patients with pancreatic pseudocyst 6 with acute pancreatitis without insufficiency and 4 with carcinoma of the body and tail of the pancreas had normal protein digestion as measured by the test It is apparent that localized disease involving the duodenal portion of the pancreatic duct may lead to insufficiency but that extensive destruction sparing the duct system and a small portion of functioning parenchyma may be unassociated with insufficiency

Comparative Fat and Fatty Acid Intestinal Absorption Test Utilizing Radioiodine Labeling Results in Normal Subjects James R Malm Keith Reemtsma and Harold G Barker[6] (Columbia Univ) propose that impaired intestinal absorption caused by digestive enzyme deficiency and by intrinsic intestinal disease can be differentiated by comparing the results of giving radioactively labeled fat and fatty acid by mouth Theoretically a normal subject should absorb both substances with enzyme deficiency fatty acid should be absorbed better than whole fat and with intestinal disease the absorption of both lipids should be impaired

Normal fasting subjects were studied after the thyroid was saturated by giving 10 drops of Lugol s solution twice daily for 2 days 5 10 ml of I^{131} tagged olive oil (about 50 μc of radioactivity) was given to 7 and tagged oleic acid to 20 One hour later breakfast was given Blood urine and stools were collected at intervals up to 72 hours Serum urine and homogenated stool were compared with a standard and results expressed in percentage of total dose given (serum volume assumed to be 4 5% of body weight)

After olive oil a peak I^{131} concentration in the serum of 14 7±4% occurred 3½-4 hours after the test meal whereas after oleic acid the peak was only 8±2 3% and was not reached until 5 6 hours Urinary excretion of radioactivity was also greater after ingestion of whole fat with 70% of

(6) Proc Soc Exper Biol & Med. 92 471-474 July 1956

the dose recovered within 24 hours 55% was recovered after fatty acid In both cases only 2-4% of the dose remained in the blood 24 hours after the test meal No explanation was apparent for the appearance of radioactivity earlier and in greater concentration in serum and urine after olive oil than after oleic acid

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► [It was emphasized above that the use of isotopically labeled substances does not, by itself endow an absorption test with any unusual qualities On the other hand tests may be designed so that advantage is taken of the isotopic label to yield information not available otherwise The preceding and following abstracts are examples of use of such technics Others (Clin Chem 2 474 1956 Proc Soc Exper Biol & Med. 94 807 1957) are also comparing the absorption of a radioactively labeled whole food with the absorption of one of its products of digestion similarly labeled to differentiate between malabsorption caused by pancreatic insufficiency and by small intestinal disease This is apparently not only theoretically promising but works in practice It must be remembered however that products of digestion if introduced into the small gut in any quantity are irritant osmotically and chemically a fact which may affect the absorption curve

The next abstract illustrates one of the available technics whereby a radioactively labeled substance is used to separate fecal material of endogenous and exogenous origin —Ed.]

Metabolic Study Following Oral Calcium[4] Administration in Patient with Nontropical Sprue is reported by Sidney Fink and Daniel Laszlo[7] (Montefiore Hosp New York)

Man 45 with history of duodenal ulcer and thromboangiitis obliterans and intermittent diarrhea was hospitalized in an exacerbation *characterized by shock watery diarrhea and tetany Hemo*globin value was 9 Gm /100 ml and serum levels were potassium 2 9 mEq/L calcium 5 2 mg and albumin 2 9 Gm /100 ml Prothrombin time was 30 seconds with a control of 11 seconds An oral glucose tolerance test showed a flat curve There was excessive fecal fat After improvement achieved by cortisone and supportive measures he was studied for 10 metabolic periods of 6 days each During the entire study vitamins A and D were given each day intramuscularly and 50 75 mg cortisone/day was given for the first half of the study

Dietary intake of about 200 mg calcium/day was supplemented by 11 Gm calcium gluconate (953 mg calcium) and on the first day of the study a single oral dose of Ca^{45} was given During the 30 days of cortisone therapy and well being urinary calcium excretion was low (6-28 mg /24 hours) fecal excretion was high (average values 414-710 mg /24 hours) calcium balances were positive throughout (average +515 mg /24 hours) and serum calcium level

(7) Gastroenterology 3 689 703 April 1957

pacted at the ampulla of Vater possibly obstructing the pancreatic ducts and the common duct Three of the jaundiced patients with normal absorption of I[131] labeled albumin had carcinoma of the ampulla of Vater The postulated explanation for normal digestion in these patients was that the tumor originated in the common duct and a separate pancreatic duct carried the secretions into the intestine

Six patients with pancreatic pseudocyst 6 with acute pancreatitis without insufficiency and 4 with carcinoma of the body and tail of the pancreas had normal protein digestion as measured by the test It is apparent that localized disease involving the duodenal portion of the pancreatic duct may lead to insufficiency but that extensive destruction sparing the duct system and a small portion of functioning parenchyma may be unassociated with insufficiency

Comparative Fat and Fatty Acid Intestinal Absorption Test Utilizing Radioiodine Labeling Results in Normal Subjects James R Malm Keith Reemtsma and *Harold G* Barker[6] (Columbia Univ) propose that impaired intestinal absorption caused by digestive enzyme deficiency and by intrinsic intestinal disease can be differentiated by comparing the results of giving radioactively labeled fat and fatty acid by mouth Theoretically a normal subject should absorb both substances with enzyme deficiency fatty acid should be absorbed better than whole fat and with intestinal disease the absorption of both lipids should be impaired

Normal fasting subjects were studied after the thyroid was saturated by giving 10 drops of Lugol s solution twice daily for 2 days 5 10 ml of I[131] tagged olive oil (about 50 μc. of radioactivity) was given to 7 and tagged oleic acid to 20 One hour later breakfast was given Blood urine and stools were collected at intervals up to 72 hours Serum urine and homogenated stool were compared with a standard and results expressed in percentage of total dose given (serum volume assumed to be 4 5% of body weight)

After olive oil a peak I[131] concentration in the serum of 14 7±4% occurred 3½-4 hours after the test meal whereas after oleic acid the peak was only 8±2 3% and was not reached until 5 6 hours Urinary excretion of radioactivity was also greater after ingestion of whole fat with 70% c

(6) P oc Soc. Expe Biol. & Med. 92 471-474 July 1956

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(7) G t oente logy 3 689 93 Apr l 1957

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(6) Proc Soc. Exper Biol. & Med. 92 471-474 July 1956

the method of Van de Kamer and related to a calculated intake according to the formula

$$CA = \frac{\text{fat intake (Gm) less fatty acids in 24 hours stool (Gm)} \times 100}{\text{fat intake (Gm)}}$$

Here C A is defined as the coefficient of fat absorption and was always above 95% in normal persons

The mean plasma carotene level in 110 normal persons was 123 µg ±47/100 ml The lower limit of normal was taken as 70 µg/100 ml though 6 who had been on restricted diets had values below this level In 30 patients with malabsorption 58 determinations were made—correlation of plasma carotene with C A was +0 45 (significant at the 1% level) Seven patients with definite steatorrhea had normal carotene levels 2 with only small areas of bowel involved by regional enteritis 3 with mild steatorrhea after gastrectomy 1 with steroid treated nontropical sprue and 1 with hepatitis in an early phase In the other 51 determinations both steatorrhea and low plasma carotene levels were found

To differentiate low carotene levels caused by dietary depletion from those due to absorptive defects 20 000 units of carotene in oil was administered daily for 1 week to 17 patients with various disorders In most a two to threefold rise was produced but levels did not return to normal in those with known absorptive disease In 8 of 10 with sprue who were on steroids simultaneous improvement in plasma carotene and fat absorption coefficient occurred Neither function improved in 2 others in whom the mechanism of steatorrhea was not established nor any effective treatment found

The plasma carotene level served as a useful technically easy and rapid screening test yielding accurate results in 103 of 110 patients without absorptive defects and in 51 of 58 determinations in 30 patients with malabsorption Patients with sprue were usually characterized by extremely low carotene levels Carotene in sprue is apparently more poorly absorbed than fat since in 4 patients levels of 0 2 3 and 9 µg/100 ml were recorded despite corresponding fat absorption coefficients of 66 61 74 and 69% Levels in patients with regional enteritis and surgically shortened small bowel were not as low probably because some absorptive capacity

was 7 8 mg /100 ml After the radiocalcium was given initial fecal loss of Ca^{45} was high but after 6 days a steady state was attained which permitted calculation of the contribution of endogenous cal cium excretion to total fecal calcium

At this point all fecal calcium[45] was presumably of endogenous origin On the assumption that Ca^{45} concentration in serum or urine was the same as its concentration in fluid excreted into the gut the ratio of the specific activity of the stools to that of serum or urine (average 0 62) was multiplied by the daily fecal calcium output to calculate endogenous fecal calcium The resultant value of 258 422 mg /24 hours was subtracted from the total fecal calcium to determine unabsorbed dietary calcium which ranged from 156 268 mg /24 hours—a 79 5% utilization of dietary calcium despite the large fecal calcium content

After cortisone withdrawal clinical relapse occurred accompa nied by a doubling of fecal calcium loss and appearance for the first time of a negative calcium balance The specific activity ratio of stool to serum urine fell Endogenous fecal calcium output stayed about the same but utilization of dietary calcium dropped to 18% Thus endogenous calcium loss in the stools stayed the same at a level 4 5 times the normal rate irrespective of the phase of the disease or whether cortisone was given Cortisone however greatly improved the absorption of dietary calcium

Measurements of urinary and fecal nitrogen phosphorus sodium and potassium and fecal fat showed that the loss of these substances in the stools was excessive as was calcium loss even in periods when he felt well and was maintained in good clinical state by cor tisone After withdrawal of cortisone fecal losses became even larger

Blood Carotene in Steatorrhea and Malabsorptive Syn dromes Julius Wenger Joseph B Kirsner and Walter L Palmer[8] (Univ of Chicago) evaluated the measurement of blood carotene (provitamin A) levels as a screening test for the malabsorption of fat and compared its reliability with fecal fat excretion and fat balance studies Carotene is a slow ly absorbed fat soluble material present in such foods as liver kidney lettuce carrots spinach tomatoes and apricots Nor mal stores are low and easily depleted by high fever steator rhea liver disease and poor diet

Plasma carotene level was determined by adding 95% al cohol and petroleum ether to plasma and reading the color of the fat soluble pigments extracted in the ether layer in a spectrophotometer *Results were expressed in μg /100 ml* according to a standardization curve obtained with crystal line carotene Fecal fat was measured in 3 day collections by

(8) Am J Med. 2 373 380 March 1957

An attempt to induce relapses was made by giving 4 patients 3 Gm gluten flour daily in capsules but the results were equivocal When 2 of these patients however resumed a normal diet diarrhea abdominal distention and distress anorexia and weight loss recurred

Two of the patients were subjected to extensive metabolic study In the control period they absorbed 35 and 54% respectively of an average fat intake (normal 92% or more)

TABLE 2—EFFECT OF GLUTEN FREE DIET ON PERCENTAGE OF TOTAL MINERAL EXCRETION

P tie	D nd D ry R me	Calc m	Ph ph ru	M gnes um	P m	Sod m
		%	%	%	%	%
S A.	S pt 18 21 gul	2 7	55	6	35	16
	S pt 24–27 gl t f	1 8	56	17	55	34
	D 26–29 gl t f	5 8	80	67	88	95
M F	J ly 18–21 g l	2 9	43	10	43	69
	J ly 4–27 gl t f	2 5	58	11	56	84
	J ly 27 30 gl t f ee	2 6	61	13	54	85
	Sept 18 21 gl t f	2 9	5	38	89	97
	M 27 30 gul	2 2	72	19	63	73
N rm l		12 SD = 2 9	57 SD = 2 1	30 SD = 2 8	78 SD = 5 9	95 SD = 3 5

N m l b t w 5 d lt t d d f 25 28 w k by Cl k D t y tak f th g p mp l t th f p t t th p ent t dy

On the gluten free diet absorption increased to 94% even though 1 patient increased fat intake to 184 Gm daily One week after reintroduction of gluten into her diet she absorbed only 76% of a 69 Gm intake Fecal nitrogen excretion which was 3 6 and 4 Gm /day before dietotherapy fell below the upper normal limit (3 Gm /day) on withdrawal of gluten Mineral metabolism also improved in that excessive fecal losses of sodium potassium magnesium and phosphorus were reversed with normal proportions of these minerals again appearing in the urine (Table 2) On the other hand despite a decreased fecal loss of calcium on the low gluten

remained Malabsorption of carotene and of fat in hepatic and pancreatic disorders paralleled one another only when the disease was extensive

► [In the diagnosis and evaluation of sprue there are few tests that excel the serum carotene level Values of less than 20 µg/100 ml are unusual except in sprue conversely patients with active and untreated sprue rarely have values above 30 µg/100 ml Because of its great technical simplicity and relative accuracy the carotene test impresses me as more useful in the clinical management of sprue than the so called tolerance tests including the recently reactivated xylose tolerance test (New England J Med 256 335 1957) As the authors point out however carotene level are less satisfactory for detecting steatorrhea in conditions other than sprue —Ed]

Effect of Gluten Free Diet on Fat Nitrogen and Mineral Metabolism in Patients with Sprue was studied by Morton K Schwartz Marvin H Sleisenger James H Pert Kathleen E Roberts Henry T Randall and Thomas P Almy[9] (Cornell Univ) The gluten free diet (Table 1) eliminates all wheat rye and oats and packaged and prepared foods must

TABLE 1—Foods to be Omitted o a Gluten Free Diet

1 Meat or fish patties or loaf made with bread or bread crumbs breaded foods canned meat dishes cold cuts unless guaranteed pure meat bread stuffing
2 Gravies or sauces thickened with wheat flour
3 Bread rolls crackers cake cookies muffins biscuits mad with rye or wheat flour waffles pancakes rusks zweiback pretzels
4 Wheat and rye cereals wheat germ barley oatmeal buckwheat kasha noodles macaroni spaghetti dumplings
5 Commercial salad dressing except pure mayonnaise
6 All canned soups except clear broth cream soups unless thickened with cream cornstarch or potato flour
7 Cakes cookies pastries commercial ice cream and ice cream cones prepared mixes puddings commercial candy containing cereal products
8 Postum malted milk Ovaltine instant coffee containing wheat beer ale

be carefully screened for fillers made of wheat Once this diet was given to 6 chronically ill patients with classic clinical and laboratory findings of nontropical sprue decrease in diarrhea abdominal distention and distress with some increase in appetite was noted in 3 patients within days and in the other 3 after several weeks As the stools returned to normal weight was gained and blood albumin calcium and prothrombin values achieved normal levels In 2 patients tested glucose tolerance was unchanged in 1 and improved in another

(9) G t oenterology 32 232 246 Febru ry 1957

mental changes skin lesions and growth defects sometimes occur out of proportion to the absorption defect and suggest that gluten may exert a direct toxic action beyond interfering with absorption This possibility is illustrated by the case of a girl 13½ with dwarfism and a minimal background of gastrointestinal symptoms When placed on a gluten free diet she rapidly grew before the enteropathy had significantly changed With respect to fat absorption this patient was unusually gluten sensitive for fecal fat content rose promptly when she was given either gluten or the glutamine containing peptide fraction After the peptide fraction was administered a glutamine containing peptide was found in abnormally large quantities in the blood It thus seems possible that in this patient the celiac syndrome produced a growth defect not only because of poor absorption of essential nutrients but because of an independent and direct effect of inadequately metabolized wheat protein

Investigations on Influence of Diet on Quantity and Composition of Intestinal Gas in Humans Since gas expands as pressure decreases a given volume at sea level will increase fourfold at 30 000 ft and 7 6 times at 40 000 ft During slow ascent such expansion of intestinal gas is no problem because of adaptive mechanisms but with rapid changes in altitude symptoms may be produced To determine whether intestinal gas formation could be affected by diet F Askevold[2] (Royal Norwegian Air Force Oslo) used a basic 2 500 calorie low cellulose diet consisting of milk sugar raw eggs and vitamins To this individual foods were added 300 Gm each of raw carrots boiled cabbage boiled potato white bread wholemeal bread boiled lean veal fat roasted mutton and boiled codfish and 150 Gm dried peas soaked and boiled Finally two diets combining several of these foods were given

Three hospitalized schizophrenic women confined to bed and willing to eat served as subjects Gas was collected by a rectal catheter connected to a fluid filled collecting vessel maintained at subatmospheric pressure by a leveling bottle The subjects ate each test diet for 14 days gas collections being made for 10 hours on the first 4 days of each week

The volume of flatus calculated/24 hours was 240-600 ml of which about 100 ml was passed at night The 5 2% carbon

(2) Sca d J Clin. & Lab. I est 8 87 94 1956

regimen calcium excretion did not return to normal possibly because absorbed calcium was used to replete severely deficient bone

The over all effect of the low gluten diet in rehabilitating patients seriously ill with sprue was striking Since the diet is well tolerated and free of side effects it appears preferable to steroid treatment

► [It should be noted that not everyone has found nontropical sprue responsive to the low gluten diet Sometimes the initial response is more favorable than the response to a second trial Nevertheless the results as here shown may be dramatic and the basic improvement achieved may be greater than that obtained with steroid therapy (see next to last abstract preceding this one) Every patient with sprue it would seem, deserves a trial with the low gluten regimen strict adherence to this diet for 3-4 weeks may be necessary before its benefits become apparent—Ed.]

Discussion on Some Problems of Steatorrhea and Reduced Stature Fractionation of gluten the protein found in wheat and rye and believed responsible for celiac disease was carried out by A C Frazer[1] (Univ of Birmingham) to determine if some portion of the gluten molecule specifically impairs absorption in celiac disease and in addition inhibits growth by a direct effect Either complete acid hydrolysis or deamidation with weak acid rendered wheat gluten harmless to celiac children On the other hand gluten subjected to in vitro peptic and tryptic digestion was still deleterious to celiac children and peptic and tryptic activity in digestive juices from celiac children is normal

Further fractionation of the enzymatic hydrolysate showed that a water soluble autoclaved peptide fraction was as toxic as whole gluten Digestion of this fraction with an extract of pig intestinal mucous membrane removed the toxic activity The harmful effect of gluten is thus not dependent on the presence of protein but is brought about by a glutamine containing peptide which presumably cannot be further digested by celiac disease patients The necessary enzymes for this activity appear to be in the intestinal wall rather than in juices secreted into the lumen This concept is consistent with the observation of van de Kamer and Weijers that the blood of celiac children contains more bound glutamine after gluten ingestion than that of normal children whether or not they have previously been on a gluten free diet

Other features of the celiac syndrome such as tempera

(1) Proc. Roy Soc. Med. 49 1009 1013 December 1956

blood Six had positive guaiac tests but 3 of these were shown to have bleeding lesions subsequently The students also tested a tarry stool from a patient with a bleeding duodenal ulcer and a stool from a subject who had eaten 1½ lb of rare steak a day for 3 days All but 2 students in the group of 116 reported a positive test in the tarry stool in the other sample only 1 student obtained a positive reaction

Neither ferrous sulfate nor rare meat taken in average portions will give a positive guaiac test for occult blood The occasional positive reports are the result of chance errors in methodology

► [Diametrically opposite statements can be found in the literature but my experience on the whole agrees entirely with that of Harvey If some ferrous sulfate tablets on the market are cracked open and exposed to the guaiac test an intense blue color results although a faint blue may be visible even before the hydrogen peroxide is added Is it not possible that tablets of this type under some conditions of intestinal hurry or other abnormal function may appear in the stool sufficiently unchanged to give a test closely resembling the positive reaction for blood? If so this would explain the occasional claim that ferrous sulfate by mouth will give a positive guaiac test.—Ed]

Virus Diarrheas of Adults and Their Possible Relationships to Infantile Diarrhea are reviewed by Irving Gordon and Elinor Whitney[4] The well known viruses seem to be unimportant causes of diarrhea whereas knowledge about those frequently causing diarrhea is fragmentary Poliomyelitis and Coxsackie viruses sometimes cause diarrhea but only in a relatively small proportion of persons harboring them Other agents (table) appear to cause diarrhea more commonly

Viral diarrheas may be classified according to whether or not fever and diarrhea are prominent symptoms A syndrome typical of the afebrile type of the disease was produced by Reimann in Philadelphia Ultrafiltered pharyngeal washings or fecal suspensions were obtained from patients with an afrebrile type of nonbacterial gastroenteritis and administered by inhalation to human volunteers Watery diarrhea nausea vomiting anorexia and abdominal pain ensued A similar syndrome is caused by the Marcy strain which after isolation was passaged serially by oral administration of bacteria free fecal filtrates One attack conferred immunity Similar results were reported in two Japanese investigations With the Marcy strain diarrhea is a prerequisite for diagnosis of the experimental disease There are natural epidemics

(4) A N w Y k A d. Sc 66 220 2 5 A g 10 1956

dioxide content on the basic diet was similar to tissue content but the oxygen content was low 0 6% Methane content was 0 4% hydrogen 2 3% and nitrogen 91 5%

It was not possible to show that individual dietary factors influenced the quantity and composition of rectal gas The basic diet should have produced the smallest quantity of gas because of its low cellulose content but the 3 subjects had test periods in which both the volume of gas and concentration of fermentation gases were lower than those measured on the basic diet Only a diet which combined 200 Gm fat meat 200 Gm wholemeal bread 200 Gm potato 50 Gm butter 50 Gm dried peas 1 egg and ½ L milk increased total gas volume moderately and concentrations of all gases except nitrogen more strikingly Possibly this diet stimulated peristalsis and because of its fat content affected the diffusion of fermentation gases

Though a vegetable and fat rich diet may affect intestinal gas to some extent so many other factors appear to influence its amount and composition that no clearcut effect of diet can be demonstrated

[See comment on page 510 —Ed]

Lack of Effect of Ingested Ferrous Sulfate on Guaiac Test for Occult Blood in Stool is described by John Collins Harvey[3] (Johns Hopkins Univ) Varying opinions are expressed by clinicians regarding the validity of tests for occult blood in the stools of patients taking iron orally Since ingested iron may color stools black it is important to know if tests for occult blood are specific In the guaiac test for occult blood a positive test is obtained when a phenol (guaiaretic acid) in gum guaiac is oxidized to quinones which yield a blue colored compound of unknown composition This oxidation is accomplished by hydrogen peroxide if catalyzed by substances such as peroxidases Because of its peroxidase like activity hemoglobin catalyzes the reaction to produce the blue colored compound signifying a positive test

Since iron does not catalyze this reaction gum guaiac would not be expected to give a blue color in the presence of iron To test this proposition 116 medical students took 0 3 Gm ferrous sulfate three times a day for three days and ate their usual diet When they tested their stools collected during this period 110 obtained negative reactions for occult

(3) Am J M Sc 23 17 19 J ly 1956

nondiarrheal in adults but diarrheal in infants and children

Significance of Viruses Recovered from Intestinal Tracts of Healthy Infants and Children is discussed by Albert B Sabin[6] (Univ of Cincinnati) The recoverable viruses vary with the method used for detection and fall into two main categories (1) those known to cause specific diseases e g poliomyelitis herpangina (Coxsackie A) epidemic pleurodynia (Coxsackie B) the pharyngoconjunctival syndrome (APC) herpes simplex and presumably infectious hepatitis mumps and influenza B (2) recently recognized viruses whose relation to various syndromes is still under investigation Among the latter are antigenically distinct orphan or human enteric viruses recently established by committee action as the enteric cytopathogenic human orphan (ECHO) group of viruses From the stools of 1 566 healthy children 1 17 31 strains of virus were isolated 25 were ECHO viruses The carrier rates diminished with increasing age

The multiplicity of ECHO virus types suggests that many years must pass before any one person has the opportunity to become infected with each Antibody against various ECHO virus types was found in 31 serums from children aged 1 5 and with greater frequency in 30 serums from medical students Although 87% of the older group had antibody for 1 or more virus only 3% had antibody for all 5

The significance of this large group of new enteric viru es is undetermined They are not a viral counterpart of the normal bacterial flora since they are rare after early life They have not been found in the stools of adult human volunteers receiving attenuated poliomyelitis viruses but have been recovered from patients with aseptic meningitis suggesting a possible etiologic relation The possible role of ECHO viruses in respiratory and enteric infections is suggested by an epidemic of rhinitis in laboratory animals and a familial epidemic of steatorrheic enteritis in man characterized by abdominal pain and frequent fatty stools The course was mild and afebrile in the parents and one older child but was relatively severe in a 3 year old An ECHO type virus was recovered from the stools and antibody developed during convalescence

To ascertain the relation of ECHO viruses to epidemic diarrhea rectal swabs were obtained in 56 children under

(5) A N w Y k Acad. S 66 26 230 A g 10 1956

however in which diarrhea occurs in a minority of cases and fever may be more prominent This is the case in epidemic nausea and vomiting or winter vomiting disease and in febrile nonbacterial gastroenteritis

Immunologic and clinical evidence suggests that afebrile (Marcy) and febrile types of nonbacterial gastroenteritis are caused by different agents In the absence of differential

PRIMARY VIRUS DIARRHEAS*

Causative Agents	Frequency of Diarrhea in Cases	
	Adults	Infants or Children
Well studied viruses		
Poliomyelitis viruses	Often	Often
Coxsackie viruses A and B	Occasional	Occasional
Incompletely studied agents		
Infectious hepatitis (hepatitis A)	Often	Regular
Afebrile nonbacterial gastroenteritis	Cardinal sign	Cardinal sign
Epidemic nausea and vomiting (winter vomiting disease)	Often	Often
Virus causing diarrhea in calves	Not known	Cardinal sign
Recently classified agents		
Enteric cytopathogenic human orphan (ECHO) viruses	See following abstract	See following abstract

* The primary virus diarrheas are considered to be those apparently associated with propagation of the virus in the intestine and the presence of infectious virus in the feces. The secondary virus diarrheas are considered to be those associated with infection elsewhere than in the gastrointestinal tract.

clinical laboratory tests diagnosis cannot be precise Nonbacterial gastroenteritis ranks second in frequency to acute undifferentiated respiratory disease in the Cleveland Family Study and recurs yearly Immunologic studies before and after the afebrile and febrile types in volunteers indicated no relation to the ARD APC or to the HE (ECHO) viruses The lack of cytopathogenic effects and cultural differences also differentiate the Marcy agent from the ECHO viruses

Pathogenic serotypes of Escherichia coli have been found in sporadic adult diarrhea but these are distinguishable from afebrile nonbacterial gastroenteritis by epidemiologic and cultural criteria Adults are less susceptible than infants to pathogenic E coli but the nonbacterial disease occurs at all ages It is therefore the probable diagnosis when there are many cases of diarrhea among adults during an outbreak of infantile diarrhea The evidence is limited but suggests that there are widespread viruses which cause diarrhea in all age groups Others like the infectious hepatitis strain and the strain causing febrile nonbacterial gastroenter —may be

rabbit serums known to contain antibodies to trichinella Over 25 presumably normal serums and serums from patients with positive Kahn tests dermatomyositis rheumatic fever and brucellosis were all negative Thus the hemagglutination test appears to be a reliable method of detecting trichinella antibodies

► [In a letter dated Apr 12 1957 Weiner states that he has continued to find the hemagglutination procedure in trichinosis highly reliable and specific The reaction is considered negative when the highest dilution of serum yielding at least a 2 reaction is no more than 1 10 —Ed]

Functional Diarrhea Analysis of Clinical and Roentgen Manifestations is presented by M H Kalser D E Zion and H L Bockus[7] (Univ of Pennsylvania) Clinical records and roentgenograms of 98 private patients with functional gastrointestinal disorders were analyzed to determine if a clinical or physiologic difference existed between patients with and without functional diarrhea Criteria for selection of patients were absence of organic disease to explain gastrointestinal symptoms and availability of x rays for review Included were patients with irritable colon functional enterocolonopathy and emotional diarrhea In one group were 69 patients with diarrhea not due to laxatives or enemas Controls consisted of 29 patients without diarrhea

Patients with functional diarrhea had no weight loss anemia or fever Emotional factors were believed responsible in 65% In 10% chronic diarrhea occurred as a sequel of acute infectious diarrhea but the chronic phase was not accompanied by systemic reactions sigmoidoscopic abnormalities or abnormal results on stool culture In 3 patients diarrhea appeared during antibiotic therapy but persisted long after this treatment had been stopped

In 11% diarrhea was continuous persisting for weeks to years the other 89% had intermittent diarrhea ranging in frequency from every few days to several times a year Some patients passed 16 20 stools a day Only 3 were wakened at night by cramps or the urge to defecate Constipation was present between exacerbations in 35% Diarrhea was accompanied by abdominal pain in 63 In 33 of these cramping pain in the lower abdomen and a strong defecatory urge preceded defecation Bowel movement afforded temporary relief

In 25 urgent need to move the bowels during or immedi

(7) G t oent logy 31 629 648 December 1956

age 4 hospitalized for diarrhea Twenty four viruses (43% positive) were found among which were 3 poliomyelitis 3 Coxsackie and ECHO viruses 12 were unidentified Although some of the viral carriers also had pathogenic enteric bacteria in the feces the high incidence of virus isolations indicates that these agents may play an important role in various diarrheal syndromes

► [People with transient but rather severe attacks of diarrhea often say or are told that they had a virus These studies indicate that the explanation may have some validity and indicate that certain syndromes can be related to specific viral agents Particularly fascinating is the description of viral steatorrhea a syndrome also observed in 13 1% of a group of English infants and children with acute gastroenteritis (Brit M J 2 339 July 28 1956) A physician friend of mine and those who took care of him became quite concerned when his stools suddenly became fatty had we known about this syndrome we could have saved ourselves a great deal of unnecessary worry —Ed]

Use of Hemagglutination in Diagnosis of Trichinosis Stella G Price and Lawrence M Weiner[6] (Wayne Univ) developed a hemagglutination test for detection of antibodies to Trichinella spiralis

METHOD —A 5% suspension of washed fresh sheep red cells in physiologic saline buffered at pH 7 2 is prepared One ml each of red cells and 1 20 000 dilution of tannic acid are mixed and incubated at 37 C for 10 minutes The cells are then centrifuged at 2 000 rpm for 10 minutes washed once in buffered saline and reconstituted with buffered saline to the original volume of the red cell suspension

One ml of extract of trichinella larvae (0 05 mg nitrogen) is added to 4 ml physiologic saline buffered at pH 6 4 and 1 ml of the suspension of tannic acid treated cells The mixture is incubated for 10 minutes at room temperature centrifuged washed once and resuspended in 1 ml saline buffered at pH 7 2 Control cells are prepared simultaneouly by substituting 1 ml saline for the larval antigen

The serum to be tested is diluted serially in saline buffered at pH 7 2 0 5 ml of each dilution is placed in a 13×75 mm tube and 0 05 ml tannic acid antigen coated cells is added to each tube The tubes are shaken and centrifuged in an International (size 2) centrifuge at 1 800 rpm/minute The tubes are removed tapped gently and read according to the appearance Grading is as follows 4 solid clumps of cells clear supernatant 3 many small clumps slightly cloudy supernatant 2, fewer small clumps cloudy supernatant 1 few small clumps turbid red supernatant 0 uniformly homogeneous suspension The titer was expressed as the highest dilution of serum yielding at least a grade 2 reaction

The hemagglutination test was 100 times as sensitive as the complement fixation reaction in detecting human and

(6) Am J Clin Path 26 1261 1269 November 1956.

Mucosal Inflammatory Spread in Diverticulitis and Ulcerative Colitis George Lumb and R H B Protheroe[8] (Cambridge England) reviewed the pathologic changes in 57 surgically obtained specimens of colonic diverticulitis Of these 21 were in an acute inflammatory phase 32 were in a quiescent stage and 4 showed complications characteristic of ulcerative colitis Each specimen in the acute phase showed an inflammatory process with superficial erosions and polymorphonuclear infiltration starting at any point in the diverticular sac spreading through the surrounding thin muscle strands and occasionally producing abscesses or fistulas Pericolic nonsuppurative peritonitis with edema congestion and thickening of the mesentery accompanied these changes Subserosal involvement was markedly greater than mucosal involvement since all changes diminished toward the mouth of the diverticulum Adjacent diverticula were frequently not inflamed Thus the normal mucosa in these cases appeared to localize the inflammatory process

In 31 of the specimens in the quiescent phase the changes were also confined to the diverticula but marked destruction and replacement by fibrous tissue made identification of diverticula difficult Mucosal flattening with round cell infiltration into the lamina propria was seen in remaining diverticula The bowel wall was thickened and there were muscular hypertrophy and proliferation of the ganglion cells of Auerbach s plexus An obliterative endarteritis and thrombosis of the adjacent vessels was common Occasionally there were foreign body giant cells with granulomatous proliferation in the subserosa In only 1 specimen was there any abnormality between the diverticula This consisted of a flattening of the mucosa with diminution in the number of crypts of Lieberkuhn and a mild lymphocyte infiltration of the lamina propria

The initial diagnosis of diverticulitis in the other 4 cases of the series had been made according to standard clinical criteria In 3 however progre sive changes including frequent passage of blood and mucus mucosal involvement on sigmoidoscopy and spread shown by x ray led to the revised diagnosis of ulcerative colitis All 4 resected specimens showed widespread muco al destruction crypt ab cesses

(8) A M.A A ch P th 62 185 193 S ptember 1956.

ately after eating was noted being so strong in some that a meal could not be eaten without interruption Certain foods were thought to cause diarrhea in 58% Raw fruits and vegetables were most commonly incriminated other foods included milk fried or fatty foods eggs spices sea food chocolate meat and alcohol Many patients probably falsely attributed to food upsets of emotional origin Achlorhydria was present in 12% of diarrhea patients and 5% of controls

Of 59 patients with diarrhea in whom barium enema films were available 67% had signs of an irritable colon, i e hypertonicity spasms and haustral irregularities Among 25 controls barium enemas showed similar signs in 75% The most pronounced radiologic difference between the two groups was transit time through the small bowel Barium was in the cecum within 90 minutes in 57% of diarrhea patients and in only 14% of controls It thus appears that many patients with functional diarrhea have abnormal small bowel function and that the name functional enterocolonopathy appears preferable to the usual designation irritable colon

► [Appendicitis was just then much in demand among better-class people on the look out for a complaint All the nervous ladies had got it on the brain if not in the abdomen thrived on it beautifully and so did their medical advisers So I drifted gradually into appendicitis and treated a great number of such cases with varied success But when the rumor began to circulate that the American surgeons had started on a campaign to cut out every appendix in the United States my cases of appendicitis began to fall off in an alarming way

It soon became evident that appendicitis was on its last legs and that a new complaint had to be discovered to meet the general demand The Faculty was up to the mark a new disease was dumped on the market a new word was coined a gold coin indeed COLITIS! It was a neat complaint safe from the surgeons knife always at hand when wanted suitable to everybody s taste Nobody knew when it came nobody knew when it went away Even today there is not seldom something vague and unsatisfactory about this diagnosis (Munthe A *The Story of San Michele* New York F P Dutton & Co Inc 1930)

Functional enterocolonopathy ? I am sure it would impress patients if it could be pronounced without stumbling Or adaptive colitis the name Almy (Am J Digest. Dis 2 93 1957) wants? More pronounceable but still fancy Perhaps one of the great advances in gastroenterologic therapy has been the trend toward debunking the importance of the bowel and its symptoms in the patient s mind Axel Munthe s countesses would not have been happy with an irritable colon but it is a name and concept most useful in explaining bowel symptoms to today s patients and therefore offering him that crucial therapeutic ingredient reassurance. Until we really know more about the pathogenesis and nature of functional bowel disorders me for irritable colon —or irritable bowel —in view of the evidence here presented that the small intestine should not be ignored —Ed]

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(8) A M A. A h P th 6 185 193 Sept mber 1956

large ragged ulcers and round cell infiltration with destruction of the muscularis mucosa Fibrosis had obliterated diverticula previously shown by x ray These 4 cases thus presented a pathologic picture of ulcerative colitis arising in an area in which diverticulitis had previously existed

In diverticulitis mucosal involvement is usually limited to the sacs but when spread does occur epithelial repair is common since the crypts of Lieberkuhn are only partially destroyed In ulcerative colitis the process is more severe and entire crypts are destroyed with production of definite ulcers Mucosal healing in the quiescent phase is inadequate in the absence of crypts of Lieberkuhn Although differential diagnosis of diverticulitis from ulcerative colitis usually is not difficult differentiation of diverticulitis with spreading mucosal lesions from localized ulcerative colitis may present problems These 4 cases raise the possibility that diverticulitis may trigger ulcerative colitis or may progress to a condition indistinguishable from it

Use of ACTH Cortisone Hydrocortisone and Related Compounds in Management of Ulcerative Colitis is reviewed by Joseph B Kirsner Manuel Sklar and Walter L Palmer[9] (Univ of Chicago) Of 180 cases treated 14 were classified

TABLE I —RESPONSE DURING INITIAL COURSE OF ACTH OR STEROID THERAPY

Steroid	Response	Total Patients	%
ACTH	Good	93	70
	Moderate	26	19
	Slight or nil	15	11
Cortisone	Good	5	36
	Moderate	5	36
	Slight or nil	4	28
Hydrocortisone	Good	14	48
	Moderate	10	33
	Slight or nil	5	19
Prednisone prednisolone	Good	0	—
	Moderate	1	33
	Slight or nil	2	67

as mild 83 as moderately severe and 83 as severe Surgical treatment had been recommended elsewhere in at least 44 Effective initial doses were aqueous corticotropin 20-40 units/24 hours intravenously or 30 units/6 hours intramuscularly hydrocortisone 200 mg orally daily cortisone

(9) Am J Med. 22 264 274 February 1957

TABLE 2—Response during Subsequent Course of ACTH or Steroid Therapy

St ro d	R po	Tot l P t t
ACTH	Good	33
	Moderate	22
	Slight or nil	13
Cortisone	Good	6
	Moderate	14
	Slight or nil	6
Hydrocortisone	Good	16
	Moderate	21
	Slight or nil	8
Prednisone prednisolone	Good	4
	Moderate	3
	Slight or nil	2
Over all response	Good	59 (40%)
	Moderate	60 (41%)
	Slight or nil	29 (19%)

Tot l ou s 148 n 91 p t ent

TABLE 3—Present Status

Normal life	37
Partial recovery course improved	76
Course unchanged following therapy	36
Surgical treatment	16
Dead	12
Lost to follow up	4
Total patients	180

teen lead u eful l

TABLE 4—Side Effects

Cushing like changes	
Minimal	43
Moderate	83
Severe	54
Electrolyte disturbances	
Alkalosis	95
Hypokalemia	43
Carbohydrate metabolic disturbances	
Hyperglycemia	24
Glycosuria	26
Psychoses (temporary)	10
Allergy to ACTH	9
Peptic ulcer	1

200 300 mg orally daily and prednisone or prednisolone 60 100 mg orally daily Corticotropin gel was used only for maintenance therapy Potassium was not prescribed routinely and sodium was limited chiefly in those receiving massive doses of ACTH General supportive measures and some sulfonamide preparation were usually employed Total initial therapy lasted less than 4 months in most trials but in 22% it lasted 4 8 months and in 7% 8 12 months

The essential results are shown in the tables After the initial treatment 91 patients required 148 repeat courses for recurrences good results being more difficult to achieve than with initial treatment and often necessitating larger doses Twenty three patients relapsed during maintenance therapy usually at low dosage levels Of 16 patients on maintenance therapy for 1 year 9 relapsed

Aqueous corticotropin used exclusively in 59 patients was the most potent and consistently effective agent With this and adrenocortical substances one may obtain a higher incidence of favorable results a smaller number of patients requiring surgery and a lower mortality rate than was possible before steroid therapy became available

Treatment of Ulcerative Colitis with Local Hydrocortisone S C Truelove[1] (Oxford Univ) used 250 mg hydrocortisone (free alcohol) dissolved in 50 ml of 50% ethyl alcohol and then added to 500 ml of 0 9% saline in patients with mild or moderate disease Starting with 125 ml and increasing up to 250 ml patients self administered the solution rectally by means of a blood transfusion set adjusted at a slow drip and equipped with a soft rectal catheter Treatments were given at home just before bedtime

Six patients given 3 week courses have been followed for a year Sigmoidoscopy and biopsy were performed before and after treatment Fifteen other courses (4 were repeat courses in relapsed cases) were carried out for 2 week periods without such close study Clinical remission was noted in 14 cases improvement in 1 and no change in 6 Sigmoidoscopic findings paralleled the clinical course improving in most but returning to normal in only 1 Biopsy however revealed no improvement in any case In some the surface epithelium appeared worse possibly due to a toxic effect of the alcohol used as the vehicle Those who responded did so within a few days Four relapses were treated several months after a successful first course 3 had a prompt remission and 1 had no response

Since the patients had mild disease many had involvement limited to the rectosigmoid The geographic extent of the colitis *did not however appear to determine responsiveness* Furthermore as judged by movement of dilute barium sus

(1) B r M J 2 1267 1272 Dec. 1 1956

pension similarly administered the therapeutic solution probably reached the splenic flexure or even higher

Four possible explanations for the apparent effectiveness of this treatment are offered (1) a local therapeutic effect was produced (2) rectal drip might be beneficial simply by lubricating the colon (3) the psychologic effect of a new form of treatment might be responsible and (4) rectally ad ministered hydrocortisone because of absorption may really act as a systemic agent

► [A few years ago we had patients with rectosigmoidal ulcerative colitis use hydrocortisone hemisuccinate in retention enemas One hundred mg of the substance which is water soluble and does not require alcohol for solution was put into 90 ml. of water one half of the amount was in stilled rectally in th mornnig and the other half at bedtime Three pa tients improved and 3 did not Results thus did not appear to warrant continued use of the method. It is also somewhat difficult to be enthusias tic about Truelove s results roughly 2 out of 3 patients with moderate ulcerative colitis respond temporarily to almost any therapeutic regimen. —Ed]

Results of Subtotal Colectomy and Ileoproctostomy in Treatment of Chronic Ulcerative Colitis were studied by Charles W Mayo and C William Broders[2] (Mayo Clinic and Found) in the records of patients so treated through 1953 Cases complicated by colonic malignancy were eliminated except 2 with carcinomas in polyps not involving the stalks 30 cases (14 in men and 16 in women) were studied Average age at initial operation was 34 (range 15-68) Disease had been present an average of 6 8 years (range 1 23)

Indications for surgery were stricture in 10 polyposis in 10 intractability in 7 perforation in 1 fistulas in 2 and pos sible malignancy in 4 Proctoscopy before surgery revealed no rectal disease in 8 pseudopolyposis in 2 fissures or rectal fistula in 6 small rectal stricture in 1 and involvement rang ing from anal scarring to active ulcerative proctitis in 13 One stage subtotal colectomy and ileoproctostomy were per formed in 16 the others having various procedures ending with the same state A variable length of terminal ileum was removed in all and 17 specimens showed involvement

Two patients could not be traced Three did not respond to a questionnaire but it was reported that 1 had had an ex ternal anal fistula 1 had had resection of a malfunctioning stoma but was well after reanastomosis and 1 was well after establishment and then closure of a proximal ileostomy One

(2) S rg Gynec & Obst 104 1 0 18 Febru ry 1957

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(1) Brit M J 2 1267 1272 Dec. 1 1956

anterior abdominal wall to serve as a safety valve In no case did leakage occur after this procedure Since later closure proved difficult at times subsequent patients underwent end to end anastomosis and temporary low ileostomy In the desperately ill patient a second method of achieving operative safety was used total colectomy followed by exteriorization of terminal ileum and proximal rectum The union of the ends which did not involve reopening the peritoneum was undertaken after clinical recovery

With these technics and strict postoperative care the mortality was 4% Postsurgical morbidity included secondary hemorrhage into the pelvis in 1 patient 5 episodes of obstruction in 3 fulminating staphylococcic enteritis in 1 fecal fistula in 1 (without the safety valve technic) fistula in ano in 1 and perianal excoriation in 4 Transient arthritis in 1 patient was the only systemic complication

In assessing results the surviving patients who had completed treatment were divided into four categories (1) 70% re established full health regained weight and returned to work and social activity (evacuations did not exceed 6 daily) (2) 15% had 7 10 evacuations daily but results were similar to those in group 1 in other respects (3) 2 aged women with weak sphincters showed results similar to those of group 2 but had more than 10 bowel movements daily (4) 8% had residual proctitis producing symptoms and required medical treatment

Proctoscopy was done repeatedly during follow up and the mucosa appeared to regenerate in all patients but those in group 4 As a result of fibrosis the rectum did not distend as does a normal rectum and the mucosa appeared fixed to underlying structures Although resolution of residual rectal inflammation occurred after total colectomy and ileorectal anastomosis the normal glandular pattern as seen on biopsy sections was *only partially regained*

► [To spare our patients permanent ileostomy ileorectal anastomosis is what we should like to have done on all of them but dare not The figures presented in the preceding 2 ab tracts do not bolster our courage Despite the emphasis on the fact that a large proportion of the patients regained weight and led active lives there were too many rectal complications and above all too many bowel movements For the advantages of having a rectum—and not necessarily a good rectum—many of the patients seemed to be paying the price of having chronic although not incapacitating disease One dreaded complication apparently was not encountered violent spread upward of the inflammatory process in the small bowel proximal to the anastomosis —Ed]

patient died 6 years postoperatively of an unknown cause and 2 had had permanent ileostomy because of persistent enterocutaneous fistulas

Of the other 22 15 had had rectal involvement before surgery Proctoscopy at follow up was normal in 5 who had had rectal stricture anal fistula anal scarring rectal ulcers or bleeding mucosa One of the 15 had not been examined postoperatively The other 9 showed continued activity including rectal polyps in 3 slight anastomotic stenosis in 1 anal fissure with inactive fistula in 1 and active proctitis in 4 Of the 7 without rectal disease before operation 4 had not been examined postoperatively 2 had no disease at proctoscopy and 1 had a small rectal stricture

Of these 22 patients 21 had gained weight and 20 were leading active lives While 20 had bowel control 2 showed slight rectal incontinence Stool production per day was 1 5 in 11 5 8 in 6 and more than 8 in 5 Stools were usually formed but soft in 8 usually loose in 12 and usually watery in 2 Slight bleeding occurred occasionally in 8

Postoperative complications consisted of recurrently draining enterocutaneous fistula in 1 rectal polyps in 4 rectal fistula in 1, anal fissure in 1 temporary ileostomy for obstruction in 1 and small bowel obstruction from adhesions in 2 Colectomy with ileoproctostomy is justifiable in some cases of ulcerative colitis if the rectum is not more than minimally involved

Total Colectomy and Ileorectal Anastomosis in Diffuse Ulcerative Colitis may be justified if it can be done with (1) low mortality and morbidity (2) return of most patients to health and work without excessive evacuations (3) resolution of rectal inflammation and (4) low risk of subsequent surgery for residual or recurrent rectal disease Stanley Aylett[3] (Gordon Hosp London) reports results with this procedure from 1951 to 1956 in 47 patients with diffuse disease which did not respond to medical management

The friable inflamed and edematous rectal end of the anastomosis if subjected to increased intraluminal pressure might be expected to disrupt or leak In early cases therefore a side to side anastomosis was done the rectum was mobilized and a temporary proctostomy wa[illegible] de on the

(3) Brit M J 1 489 492 Mar 2 1957

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Arterial Hemorrhage from Large Bowel Diverticulum is described by Edwin P Maynard III and Arthur B Voorhees Jr[4] (Columbia Univ) The incrimination of diverticula as a cause of intestinal bleeding is usually based on circumstantial evidence inferred from the absence of other evident disease in resected specimens In a few cases stronger evidence has been presented such as pooled blood in the diverticulum or an apparent direct communication with submucosal vessels In no previously reported case has active bleeding been seen to originate in a diverticulum

White man, 60 had had 8 episodes of major rectal bleeding in 4 years preceding hospitalization Transfusions had been required occasionally and the bleeding had stopped spontaneously During the 9th bleeding episode he required 6 000 ml blood in 5 days Barium enema studies showed only diverticulosis and sigmoid diverticulitis At exploration the bleeding site was not identified but there was no further bleeding after an inflamed area in the sigmoid was resected He was well for 3 years then bleeding recurred As 7 000 ml blood was required in 19 hours exploratory operation was repeated There was no gross evidence of diverticulitis *Blood* was stripped out of the colon into the rectum and rubber shod clamps were placed along the colon at 10 cm intervals Within a few minutes one segment in the transverse colon became filled with blood When the bowel was opened blood was flowing from the ostium of a diverticulum A bleeding artery was identified when the diverticulum was inverted into the bowel The artery was transfixed and no further bleeding has occurred

Proctosigmoidoscopy in General Physical Examination E L Crumpacker J P Baker H C Ballou E J Morhous and J M Emmett[5] (Greenbrier Clinic White Sulphur Springs W Va) performed 5 158 proctosigmoidoscopies in 2 401 unselected men as part of routine annual examinations The incidence of polyps on the first and repeated examinations is shown in the table Polyps were found in 161 patients *(6 7%) 2 to many polyps were seen in 48 of these and 3 had* previously unsuspected multiple polyposis of the colon Apparently new polyps developed at the rate of approximately 2%/year The reported frequency is lower than the true incidence since some patients had polyps previously removed elsewhere and some small polyps were undoubtedly missed

Although recommendations were made that all polyps be

(4) Ga t oenter logy 31 210 211 F bru ry 1956
(5) A M A Arch I t Med 98 314 3 0 September 1956

removed pathologic reports on only 53 were available Of these 36 were benign adenomatous polyps 8 contained invasive carcinoma 8 were called "carcinoma in situ" hyperplastic polyps or atypical hyperplasia and 1 was a carcinoid Double-contrast barium enema examinations were performed on 110 of the 161 patients 14 showed definite polyps higher in the colon 6 had probable small polyps and 1 had an annular carcinoma.

Only 4 of all the polyps were felt by rectal digital examination although 40 were less than 10 cm from the anal margin. Seventeen patients gave a history of rectal bleeding some of which was hemorrhoidal in origin.

Proctosigmoidoscopy is the only reliable technic for ex

INCIDENCE OF POLYPS DISCOVERED BY 5158 PROCTOSIGMOIDOSCOPIC EXAMINATIONS OF 2401 PATIENTS

ANNUAL EXAMINATION	NO. OF PATIENTS EXAMINED	NO. PATIENTS WITH POLYPS (%)
1st	*2401*	*94 (3.9)*
2d	1183	43 (3.6)
3d	764	19 (2.5)
4th	470	10 (2.2)
5th	225	5 (2.2)
6th	87	2 (2.3)
7th	48	1 (2.1)
Total examinations	5158	161 (6.7 total patients) (3.1 total examinations)

amination of the rectum and low sigmoid and with it more potentially serious yet correctable diseases may be detected than by other routine procedures Double-contrast barium enema examination is obligatory when polyps are detected *since in this series a higher lesion was found in 1 of 7 patients* with proctosigmoidoscopically identified polyps

► [This has been a popular subject this year In 50 000 asymptomatic patients examined at the Cancer Prevention Center of Chicago (J.A.M.A. 163 411 Feb 9 1957) polyps were found in 7.9% and cancer in polyps in 0.65% In 500 completely asymptomatic males age 17 25 years examined by proctoscopy benign rectal polyps were found in 1.6% cancer was found in none (Gastroent. 32 704 1957)

Once the polyp is discovered, the next question is what to do about it. As Marie Ortmayer points out, the clinician is handicapped by the "confusing state of diagnosis among outstanding pathologists No practical methods exist at present to determine if benign, precancerous and noninvading cancerous human tumors possess biologically inherent

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(4) Gastroenterology 31 210 211 February 1956
(5) A.M.A. Arch. Int. Med. 98 314 320 September 1956.

were in patients under age 40 An average follow up of 5 years after local excision with or without fulguration of the base disclosed no recurrence but this is a short follow up for slowly progressing carcinoids

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LIVER AND GALLBLADDER

Direct Reacting Bilirubin Bilirubin Glucuronide in Serum Bile and Urine Rudi Schmid (Nat l Inst of Health) analyzed bilirubin pigments to determine the factors that permit separation of these pigments into the direct and indirect reacting fractions by means of the van den Bergh reaction The natural bilirubin pigments which are very labile were first converted to more stable azo compounds by adding an excess of diazotized sulfanilic acid in hydrochloric acid to bilirubin containing fluids Two such azo bilirubin pigments were obtained and separated from serum urine and bile by ascending paper chromatography one A was obtained from indirect reacting serum bilirubin crystalline bilirubin and heated bile the other B was obtained from direct reacting serum bilirubin urine and fresh bile Azo pigment B (from direct reacting bilirubin) was converted to pigment A (indirect) by acid hydrolysis with liberation of glucuronic acid Thus direct reacting bilirubin consists of bilirubin usually coupled with two molecules of glucuronic acid though small amounts of the monoglucuronide may also exist Indirect reacting bilirubin is free unconjugated bilirubin Since almost all azo pigment recovered from the urine of jaundiced patients is type B the kidneys apparently excrete only conjugated bilirubin

The direct van den Bergh reaction is given by bilirubin conjugated with glucuronic acid a compound that is extremely water soluble Unconjugated bilirubin (indirect reacting) because of its insolubility in water requires addition of alcohol to initiate diazo coupling In bile most bilirubin is water soluble glucuronide In regurgitation jaundice this conjugated bilirubin enters the blood and is excreted by the kidneys resulting in bilirubinuria

➤ [Why one bil rubin pigment in human blood gives a direct van den Be gh reaction and another the indirect reaction has been looking for an

(7) S en 124 76 77 J ly 13 1956

invading tendencies (Gastroenterology 31 404 1956) In this situation the report of Turnbull is reassuring In 46 patients benign appearing rectal or colonic polyps were ablated by coagulation with or without radon seeds and occasionally by snare In each instance there was definite histologic evidence of cancer i e carcinoma in situ or superficial carcinoma At follow up 4 15 years later however only 1 was known to have died of a diffuse carcinomatosis and the source of this was undiscovered. Turnbull thus argues that benign appearing polyps pursue a benign clinical course regardless of the histologic picture presented (Postgrad Med. 21 365 1957)—Ed.]

Submucosal Rectal Nodules Clinicopathologic Review of submucosal nodules removed surgically from the rectum is presented by Frank C Swartzlander Raymond J Jackman and Malcolm B Dockerty[6] (Mayo Clinic and Found) In 91 patients examined from 1945 to 1951 lymphoid hyperplasia of unknown etiology was the commonest lesion occurring in 28 Multiple nodules were seen in one third The lesions ranged in diameter from 3 mm to 4 cm and all were found by either digital or proctoscopic examination No patient had generalized lymphoid disease Twelve patients were re examined after 1 10 years and generalized lymphoid disease or lymphosarcoma had not developed

Oleomas occurred in 20 patients and were grossly indistinguishable from other submucosal nodules Twelve patients had undergone injection or rectal surgery and the interval between injection and discovery of the nodule ranged from 6 months to 6 years

Carcinoids were found in 16 patients and ranged from 3 mm to 1 5 cm in diameter The color varied from yellow to white Most were not characteristically yellow but when a lesion was yellow tinged it was usually a carcinoid The mucosa was intact in all lesions except one which previously had been biopsied and treated with radium Twelve patients were examined 1 5 years later and there were no recurrences

Five patients had leiomyomas all within 3 cm of the dentate margin The average diameter was 1 5 cm Only 1 submucosal nodule proved to be a leiomyosarcoma and a grade I adenocarcinoma was found in a patient with multiple colonic carcinomas

Submucosal nodules of the rectum are not uncommon Most are described on the anterior wall probably because this wall is more thoroughly examinable during proctoscopy than the other sides Eighteen (19 9%) nodules proved to be malignant of which 16 were carcinoids Six of the latter

(6) Am J S rg 9 657 665 Novembe 1956

were in patients under age 40 An average follow up of 5 years after local excision with or without fulguration of the base disclosed no recurrence but this is a short follow up for slowly progressing carcinoids

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LIVER AND GALLBLADDER

Direct Reacting Bilirubin Bilirubin Glucuronide in Serum Bile and Urine Rudi Schmid[7] (Nat l Inst of Health) analyzed bilirubin pigments to determine the factors that permit separation of these pigments into the direct and indirect reacting fractions by means of the van den Bergh reaction The natural bilirubin pigments which are very labile were first converted to more stable azo compounds by adding an excess of diazotized sulfanilic acid in hydrochloric acid to bilirubin containing fluids Two such azo bilirubin pigments were obtained and separated from serum urine and bile by ascending paper chromatography one A was obtained from indirect reacting serum bilirubin crystalline bilirubin and heated bile the other B was obtained from direct reacting serum bilirubin urine and fresh bile Azo pigment B (from direct reacting bilirubin) was converted to pigment A (indirect) by acid hydrolysis with liberation of glucuronic acid Thus direct reacting bilirubin consists of bilirubin usually coupled with two molecules of glucuronic acid though small amounts of the monoglucuronide may also exist Indirect reacting bilirubin is free unconjugated bilirubin Since almost all azo pigment recovered from the urine of jaundiced patients is type B the kidneys apparently excrete only conjugated bilirubin

The direct van den Bergh reaction is given by bilirubin conjugated with glucuronic acid a compound that is extremely water soluble Unconjugated bilirubin (indirect reacting) because of its insolubility in water requires addition of alcohol to initiate diazo coupling In bile most bilirubin is water soluble glucuronide In regurgitation jaundice this conjugated bilirubin enters the blood and is excreted by the kidneys resulting in bilirubinuria

➤ [Why one bil rub n pigment in human blood gives a direct van den Bergh reaction and another the indirect reaction has been looking for an

(7) S 124 76 77 J ly 13 1956

invading tendencies (Gastroenterology 31 404 1956) In this situation the report of Turnbull is reassuring In 46 patients benign appearing rectal or colonic polyps were ablated by coagulation with or without radon seeds and occasionally by snare In each instance there was definite histologic evidence of cancer i e carcinoma in situ or superficial carcinoma At follow up 4 15 years later however only 1 was known to have died of a diffuse carcinomatosis and the source of this was undiscovered Turnbull thus argues that benign appearing polyps pursue a benign clinical course regardless of the histologic picture presented (Postgrad Med 21 365 1957) —Ed]

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(6) Am J Su g 9 657 665 Novembe 1956

The difference between those with and those without IHC in postnecrotic and alcoholic cirrhosis was also chiefly that of cellular bile imbibition

Intrahepatic cholestasis following chlorpromazine showed centrilobular bile stasis with large bile casts in the canaliculi

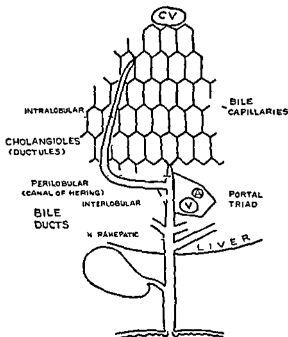


Fig 93—S h m t c d w g f n rm l b l y pa g (Court y f P pp H nd S to, P B G st oe t l gy 31 683 700 D cemb 1956)

and moderate bile imbibition in the liver and Kupffer cells Parenchymal cells showed little necrosis but portal tracts appeared edematous and infiltrated with lymphocytes large monocytes and a sprinkling of eosinophils Similar findings with more eosinophils were features of IHC following para aminosalicylic acid

Pure cholestasis with jaundice of less than 2 months and no known drug exposure showed centrilobular bile stasis some atrophy of liver cell plates and no significant liver cell

explanation for nearly 50 years The first break came when it was shown that the difference could not be accounted for on the basis of protein binding (1954 55 YEAR BOOK p 497) In 1956 within the short pace of a few months the answer was forthcoming from three widely separated and independent sources Billing and Lathe in England (Biochem J 63 6P 1956) Talafant in Czechoslovakia (Chem. Listy 50 817 1956) and Schmid in Washington

The real explanation of the difference between the bilirubin pigments with respect to the van den Bergh reaction and their urinary excretion is much simpler than some of the fanciful explanations previously entertained Conjugation with glucuronic acid is a well recognized function of the liver crucial not only for detoxification as in the case of phenolic compounds but also in the normal hepatic metabolism of adrenocortical steroids Thus conjugation of tetrahydrocortisone with glucuronic acid yields a water soluble and hence excretable compound. Those versed in the old terminology however will have to make a complete about face. Obviously what used to be known as combined bilirubin is actually free bilirubin i e the water insoluble pigment which has not yet been conjugated The pigment which has been acted on by liver cells and formerly identified as free is obviously combined i e it is conjugated with glucuronic acid.

The biochemical identification of the two bilirubin pigments is not only of academic interest as it undoubtedly will help explain the nature of various types of jaundice In Gilbert s syndrome (constitutional hepatic dysfunction familial nonhemolytic jaundice) for example the icterus may be related to abnormal function of the enzyme systems responsible for bilirubin conjugation Two components of this system have been tentatively identified Apparently glucuronic acid has to be made active" with uridine diphosphate and a transferase is necessary to complete the conjugation of uridine diphosphoglucuronic acid with bilirubin —Ed.]

Intrahepatic Cholestasis (Cholangiolitis) also called intrahepatic biliary obstruction produces clinical and laboratory findings identical to those of extra hepatic biliary obstruction (surgical jaundice) To study the morphologic basis of intrahepatic cholestasis (IHC) and its pathogenesis Hans Popper and Paul B Szanto[8] *(Cook County Hosp)* *compared hepatic autopsy and biopsy specimens from cases* of IHC with those from cases of liver disease without IHC and those from cases of extrahepatic biliary obstruction

In nonfatal viral hepatitis the intensity and incidence of hepatocellular degeneration acidophilic changes single cell *necrosis and Kupffer cell mobilization* were equal in cases with and those without IHC Slightly more portal cellular infiltration and ductular (cholangiolar) proliferation occurred when IHC was present but the major differences were bile plugs in the canaliculi (bile capillaries) and cellular *bile staining in IHC Bile plugs (microcalculi)* in the ductules were seen only exceptionally more so in fatal cases

(8) Gastroenterology 31 683 700 December 1956.

Chemical characteristics are uniformly obstructive ren dering differentiation from causes of extrahepatic biliary obstruction difficult and leading to exploratory surgery in 25% of reported cases The histopathology is characterized by bile stasis periportal inflammatory cell infiltration and parenchymal regeneration Limited observations suggest that eosinophils in the periportal infiltrate are an early find

SUMMARY OF CLINICAL FEATURES

	Tw Tw O C s	Tw N Y S VE C M H LI E
A ag t t l d se	1 260 mg (g 10 5 700)	1 2 3 g (g 38 8 0)
A ge d t n f therapy	15 d y	17 6 days
I t l f m fi t d t set f p od m	14 d y (g 6 4)	14 7 d y (g 5)
I t rv l f m fi t d t on et of j d	18 6 d y (g 11 29)	20 d y (g 6 30)
A g d tion f j d	30 day (g 7 1 2)	43 d y (g 7 156)

	I c c IN O C		I C M H LITERATUR	
	No	ơ	N	%
P d m l ympt m	20	91	21	78
fev	15	68	13	48
h ils	8	36	8	27
ea	5	23	14	52
omit g	5	23	7	26
bd m l p n	12	55	8	30
p t	13	59	19	70
J d	20	91	27	100
P l[bl l	18	8	17	63
T d l	5	23	9	33
P lp bl pl n	0	0	1	4
El ted m b l b	21	95	24 (f 24)	100
El t d m lk l ph ph t	21	95	24 (f 24)	100
P t ph l n floc l t t t	0	0	0	0
Hyp gl bul m a	0	0	2	7
E ph l (p ph l bl od)	14 (f 17)	8	8 (f 9)	89
E pl t ry l p ot y	1	5	7	26

At 2+

ing Two cases reported in the literature have shown paren chymal damage and 1 slight periportal fibrosis

Jaundice may persist for 4 months but all patients have recovered Although 6 fatalities have been recorded in none was death unequivocably attributable to chlorpromazine jaundice

The normal caliber and appearance of the major bile ducts argue against common duct obstruction as a cause of the jaundice The interval between chlorpromazine administra tion and systemic prodromas reported accelerated reaction

damage Coarse bile plugs and extracanalicular bile droplets surrounding cells with feathery degeneration were noted In jaundice of longer duration bile deposits extended to the rest of the lobule and both peri and intra lobular ductules were increased in number dilated and contained microcalculi Around them inflammatory exudate and fibrosis were sometimes noted

Comparable stages of extrahepatic biliary obstruction exhibited for the most part few qualitative differences from those of pure IHC In a few cases however features were found that occur only in extrahepatic biliary obstruction These were (1) dilatation and sometimes proliferation of the septal bile ducts which might contain bile concrements (2) extravasation of bile which created a foreign body surrounded by granulation tissue in the portal tracts and (3) large areas of cells with reticulated cytoplasm and poor nuclear staining adjacent to portal tracts (bile infarcts) Only if these features are found can IHC and extrahepatic biliary obstruction be differentiated reliably by biopsy (Fig 93)

The postulated course of events in the pathogenesis of IHC is that first increased ductular permeability as a result of various causes permits bile to seep into surrounding tissues and blood Because of fluid loss elements precipitate and form microcalculi which may add an obstructive feature Eventually the leaking bile irritates periductular connective tissue initiating an inflammatory reaction and finally collagen formation

► [Because of the galaxy of names applied to various arborizations of the biliary system the uninitiated may find it difficult to follow a pathologist as he describes changes in the conduits that drain bile from the liver Popper and Szanto well alert to this communication problem do their best to be specific The tiny tubes that collect bile from the polygonal cell are bile *capillaries* or *canaliculi* These join to form slightly larger channels the *cholangioles* or *ductules* which may originate as *intralobular* structures but thence course into the *perilobular* spaces where they merge to form *interlobular bile ducts* (Fig 93) —Ed.]

Chlorpromazine Jaundice Analysis of 22 Cases From personal observation and review of the literature the clinical features of chlorpromazine jaundice seem quite uniform to J Lawrence Werther and Burton I Korelitz[9] (*Mount Sinai Hosp New York*) The syndrome occurs about 2 weeks after initial exposure and is unrelated to total dose or previous liver disease The salient features are listed in the table

(9) Am J Med. 2 351 366 M rch 1957

course of the illness and in 1 pericarditis pleural effusion and a few L E cells were demonstrated Arthralgias appeared in 11 patients and occasionally were associated with febrile episodes and flare ups of the liver disease In three chronic joint changes resembling those in rheumatoid arthritis en sued

Elevated levels of serum gamma globulin the highest re corded at 9 4 Gm /100 ml were found in all cases but these diminished with progres of the liver disease The gamma globulin was normal by immunochemical and zone electro phoretic technics Plasmacytes in the bone marrow were morphologically and numerically normal but were seen in the liver sinusoids and spaces of Disse The numbers of these cells appeared to be correlated with the serum gamma glob ulin level and the acute stages of the disease

Increased excretion of adrenocortical reducing steroids in the urine appeared in some cases and elevation of serum bilirubin after estrogen administration occurred in three of five patients Treatment with cortisone in the acute stages of the disease reduced fever and respiratory and cardiac signs Continuous therapy with small doses caused symptomatic improvement and reduction in hepatosplenomegaly serum bilirubin and gamma globulin In 2 patients withdrawal of cortisone led to relapse

Although antecedent viral hepatitis could not be excluded entirely in 7 no apparent cause of the disease was found in the rest of the 26 cases The syndrome described which ex hibits similarities to collagen diseases may develop because endocrine factors in young women modify the usual course of infectious hepatitis

Lupoid Hepatitis Ian R Mackay L I Taft and D C Cowling[2] designate as lupoid hepatitis a syndrome char acterized by the finding of L E cells in the blood and the clinical and biochemical features of prolonged jaundice py rexial episodes hepatomegaly striking splenomegaly spider angiomas occasional ascites low serum albumin level ele vated gamma globulin level positive flocculation test and a rapid erythrocyte sedimentation rate

Of 7 cases reported 4 were in young women 2 in older women and 1 in a young man Hepatic biopsies showed fibro

(2) La et 2 1323 1326 Dec. 29 1956

if the drug is tried a second time and lack of relationship between occurrence of jaundice and size of dose favor an idiosyncratic or allergic response

► [The number of patients who have died as a result of chlorpromazine hepatitis is a moot point When chlorpromazine is given to a severely ill patient who then dies in a jaundiced state it is obviously difficult to disentangle the various causes and to apportion responsibility with assurance For this reason some will say that they know of 7 or 8 cases of deaths from chlorpromazine hepatitis whereas others will take the position adopted by the authors of this abstract.—Ed]

Problem of Chronic Liver Disease in Young Women A G Bearn H G Kunkel and R J Slater[1] (Rockefeller Inst) studied 26 patients with an unusual form of cirrhosis of the liver characterized by insidious onset endocrine abnormalities arthralgia febrile episodes hypergammaglobulinemia progressive course and unknown etiology The predominance in women was striking (88 5%) and age of onset ranged from 3 to 33 years (average 15 years) Delayed menstruation and amenorrhea were frequent and often preceded recognition of liver disease Purplish striae acne hirsutism obesity and moon facies reminiscent of Cushing s syndrome were less common early findings but hypertension and osteoporosis did not occur Occasionally the disease began with an obscure febrile episode or arthralgia and rarely with a transient erythematous rash

Symptomless jaundice was often the first sign of hepatic disease although biochemical evidence of severe cirrhosis was found usually on the first examination Characteristically the patients were well nourished but with progression the classic signs of cirrhosis became increasingly apparent The spleen was usually enlarged considerably and rarely was the site of minor infarction Esophageal varices were shown by x rays in 12 cases Spider angiomas developed in most patients but ascites was uncommon until late in the disease Death within 10 years from esophageal hemorrhage or hepatic coma was the rule but some patients led active lives for 11 20 years One male made a clinical recovery Of the 25 patients with continuing disease 12 died At autopsy a nodular moderately enlarged liver resembling classic post necrotic cirrhosis was usually found

Febrile episodes sometimes associated with cardiac or respiratory symptoms occurred in 10 patients during the

(1) Am. J M d. 21 3 15 J ly 1956

markedly dilated (Fig 94) The count was 75 in 1 case of fatal viral hepatitis with ascites Though all cases of ascites in this group had increased numbers of lymphatics with di



Fig 94 (top) —D lat d lymph t ca f ong t h rt f l w h sc t H mat yh -e ×3
Fg 9 (bottom) —D lat d d th k w ll d lympha case f pos ec ot hos w th sc H m t xyl eos n ×3
(Courtesy f B gg to A. H and C J C New E gl d J M d 6 531 535 M h 21 1957)

ameters larger than normal the walls were thin and howed no signs of inflammation

In 30 cirrhotics with ascites mean counts were 55 (24 100) with no difference apparent between alcoholic and postnecrotic cirrhosis The lymphatics were large and their walls thickened by fibroblasts lymphocytic infiltration and muscular hypertrophy (Fig 95) In 10 cirrhotics without

sis nodular regeneration and cellular infiltration but 1 young woman was a chronic alcoholic and 1 elderly woman died of gastric cancer One patient had a rash a second arthralgia and a third both conditions

To explain this syndrome the authors suggest that liver cells as the result of injury may become antigenic and stimulate *circulating or cell borne antibodies These antibodies* may then lead to perpetuation of the hepatitis and occasionally to lupus erythematosus with L E cells in the blood

► [The problem presented by the 2 preceding abstracts is whether medical knowledge is served by selecting variants of a disease or of diseases and then lumping them together because they present at least superficially a clinical syndrome From the purely clinical viewpoint this question must be answered in the affirmative for the various possible manifestations of liver disease deserve emphasis On the other hand the danger exists that various conditions unrelated etiologically or pathogenically will be amalgamated into a contrived whole merely on the basis of certain superficial *similarities It has been known for years that certain cases of* otherwise classic viral hepatitis may exhibit joint and skin symptoms Should these phenomena plus the discovery of an isolated laboratory sign (i e and L E cell) make us consider the disease process the same as that of a patient with alcoholic cirrhosis who happens to have the same laboratory abnormality as well as dermatologic or arthritic phenomena? Doubt is heightened by a report that a biologic false positive L E test may occur in hepatic disease (New England J Med 254 1160 1956) —Ed]

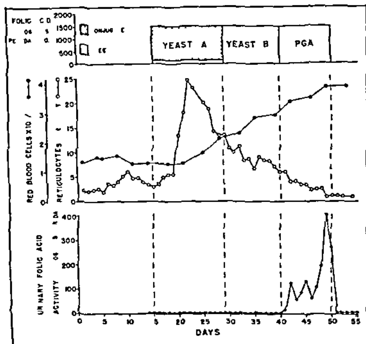
Hepatic Hilar Lymphatics of Man Their Relation to Ascites Archie H Baggenstoss and James C Cain[3] (Mayo Clinic) prepared cross sections of the hepatoduodenal ligament *counted the total number of lymphatics* with a scanning lens (magnification ×32) and noted the characteristics of the lymphatic walls In 100 consecutive autopsy cases without ascites the number of lymphatics averaged 34 (6 87) The mean number in 25 cases with moderate to severe passive congestion of the liver was 40 and in all but 3 of 12 cases with lymphatic counts above 50 there was passive hepatic congestion Average counts in other disorders were 38 in centrolobular liver necrosis 29 in focal hepatic necrosis *30 in fatty liver 33 in diabetes and 35 in uremia* In 2 cases of sudden traumatic death counts were 19 and 33 Generally dilatation of lymphatics accompanied increased counts

In 28 cases with ascites due to congestive failure carcinomatosis renal disease and noncirrhotic liver disease the average number of lymphatics was 50 (26 87) In 18 with congestive failure counts averaged 49 and the channels were

(3) New E gla d J M d 256 531 535 Mar 1 1957

tissues in the 4 anemic patients were depleted of folic acid

Serum vitamin B_1 levels in all patients approximated the normal mean value of 532 ± 161 µµg /cc and greatly exceeded the range of 0 85 µµg found in pernicious anemia In 11 of the 16 patients the blood buffy coat contained no



F g 9 —R ponse f pat ent w th hepatic hos d megal bla t em to va ou f l d p eparat on Sponta eou mall ease in eticulocyt act vity occu d d g p od f ba l d t, ft wh h dm trat on f t l sou ce of f l c id (yea t A) wa ttended by strik g ret locyt esponse d rea g hemoglob f l N f rth h m t logi r ponse ttend d th rapy w th deconj gated fol d (yea t B) w th synthet f l a d (PGA) (Courtesy of J dl, J H a d Le A. A. Ann. I t Med. 45 1027 1044 Decembe 1956)

ascorbic acid but 1 had clinical signs of scurvy No reticulocyte rise occurred in 2 patients who received 1 Gm oral ascorbic acid

The morphologic features of the anemia apparently attributable to folic acid deficiency were not specific The deficiency of folic acid in the 4 patients could not be ascribed to

ascites lymphatics were similarly increased (mean count 49) and displayed thick walls

The increased numbers of lymphatics observed in these groups probably reflects the opening of potential channels rather than the formation of new vessels Since these channels in the hepatoduodenal ligament are the main lymphatics draining the liver they enlarge when venous stasis is produced by congestive failure or intrahepatic portal hypertension *The increased thickness of the lymphatic walls in cirrhosis* is an indication that lymph has been flowing under increased pressure long enough to produce muscular and fibrotic hypertrophy but inflammation may also play a role

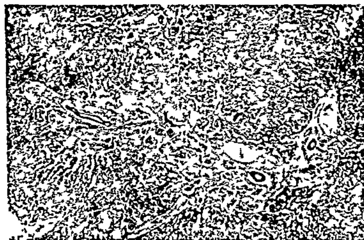
► [The difference in the walls of hepatic lymphatics in the ascites of cirrhosis and that of other conditions raises further questions as to the causes of peritoneal fluid accumulation in cirrhosis Is it merely a matter of hydrostatic and osmotic pressures or may the cirrhotic process actually involve and damage the lymphatic drainage system of the liver?—Ed.]

Metabolism of Folic Acid in Cirrhosis James H Jandl and Arnold A Lear[4] (Harvard Med School) studied 16 cirrhotic patients with alcoholism and anemia not caused by blood loss to determine if the blood picture reflected a deficiency of folic acid citrovorum factor vitamin B_{12} or ascorbic acid Folic acid when given orally was administered in both the natural conjugated and the enzymatically liberated free form

In 12 patients with hemoglobin levels of 5 1 13 Gm /100 cc and only moderate macrocytosis neither oral nor parenteral administration of folic acid (synthetic pteroylglutamic acid) elicited a reticulocyte response In 4 with severe anemia (hemoglobin 2 9 5 7 Gm /100 cc) more pronounced macrocytosis and maturation disturbance of red and white cell precursors folic acid caused prompt clinical and hematologic improvement Two were given 250 500 μg pteroylglutamic acid subcutaneously daily with reticulocyte rises of 26 and 22% on the 6th and 10th days of therapy respectively The 2 others who were given yeast containing 1 350 μg conjugated and 150 μg free folic acid also exhibited striking reticulocyte responses (Fig 96) In contradistinction to the first 12 patients the 4 in the second group did not achieve maximum excretion of folic acid in the urine until 3-4 weeks after beginning treatment further proof that the

(4) Ann I t M d 45 1027 1044 D c mber 1956

The diagnosis of cirrhosis was established by biopsy in 5 and clinically in 2 Focal biliary cirrhosis is the initial lesion and is characterized by concretions of amorphous eosinophilic material plugging the bile ductules biliary proliferation inflammatory reaction and absence of marked bile stasis in the surrounding parenchyma The concretions resembling those seen in the pancreas are initially located at the junction of the cholangioles and the small bile ducts at the periphery of the portal spaces Inspissated material may ex



Fg 97—Bl d t p l f t d fl mmat ry filt t d fib os t d g n fl t f h on long b l d ct d h la g le (Court y f d S t Agnese, A d Bl W A P d t 18 387 409 Sept mb 1956)

trude into interstitial connective tissue and appears to induce an acute inflammatory reaction The focal lesions appear to extend by bile duct proliferation and fibrosis along cholangioles with minimal lobule invasion (Fig 97) As the disease progresses the foci coalesce with extension of fibrosis and atrophy of the intervening hepatic parenchyma Typical are irregular nodules larger than those of portal or biliary cirrhosis and the absence or moderate degree of bile stasis in the parenchyma The histologic appearance of this multilobular biliary cirrhosis with concretions suggests that it is initiated by obstruction of bile ductules by inspissated secre

clearcut dietary inadequacy impaired digestion of natural conjugated folic acid deficient absorption failure of conversion of folic acid to citrovorum factor or inability to utilize folic acid Possibly increased requirements explain why in some patients with alcoholic cirrhosis the usual hemolytic type of anemia is complicated by a superimposed anemia of folic acid deficiency

An average hospital diet contains 1,000 1 500 µg natural folic acid Of this natural conjugated form about 25% is absorbed whereas 60% of free folic acid and 95% of the synthetic form is absorbed It seems probable that 200 300 mg pteroylglutamic acid constitutes adequate daily therapy for an adult

► [Not only informative about liver disease but many pearls about folic acid!—Ed]

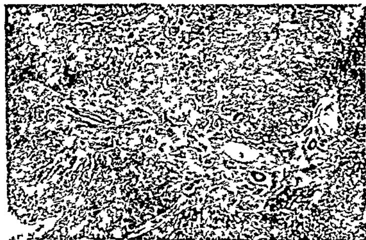
Distinctive Type of Biliary Cirrhosis of Liver Associated with Cystic Fibrosis of Pancreas Recognition through Signs of Portal Hypertension is described by Paul A di Sant Agnese and William A Blanc[5] (Columbia Univ) Seven white children (4 boys) have been observed with cystic fibrosis of the pancreas and clinically manifest cirrhosis of the liver They were aged 4 10 when liver disease was first recognized Sodium and chloride concentration in the sweat was increased in all 5 had pancreatic insufficiency and in 2 pulmonary involvement was not clinically evident at the time cirrhosis was diagnosed but developed subsequently

Hepatosplenomegaly was present in all In 4 patients shunting operations were performed because of greatly elevated portal venous pressures measured at operation Of the 7 3 are dead 2 of progressive pulmonary disease and 1 of gastrointestinal hemorrhage following thrombosis of a splenorenal shunt Of the 4 living patients pulmonary status is deteriorating in 2

Serum albumin levels bromsulfalein retention and other blood chemical data were normal Zinc turbidity values were high varying with the degree of pulmonary disease and cephalin flocculation and thymol turbidity tests were positive in 3 Thrombocytopenia was present in all but platelets returned to normal in those who underwent a shunting operation

(5) P d tr c 18 38 409 1956

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F g 97 — B le d ct pr l ferat on d flammatory filtrat nd fib os tend g n st ll t f hion long bile duct and ch la gioles (Court y f d S t Agnese, A nd Bla W A Ped t c 18 387-409 S pt mber 1956)

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(5) Ped tr 18 387 409 1956

Chlortetracycline in the medium decreased NH_4 production in relation to growth of Bact aerogenes and a hemolytic strain of Streptococcus faecalis It had no effect on Bact coli Bact freundii P morganii P vulgaris P mirabilis and Lactobacillus plantarum and augmented NH_4 production by a microaerophilic streptococcus

Proteus mirabilis produced the most amines and casein was the best medium for amine production by all species Chlortetracycline prevented amine formation by Bact freundii and Bact aerogenes but had little or no effect on hemolytic Str faecalis and P mirabilis

The volume and bacterial content of gut fluid are unknown and in vivo intestinal ammonium production cannot be measured Since in this study bacterial cell nitrogen was of the same magnitude as NH_4 nitrogen produced and since the daily nitrogen content of feces is 1 3 Gm in vivo NH_4 production may be in the order of grams rather than milligrams

Patients with cirrhosis of the liver have increased numbers of coliform bacteria and Str faecalis in the small intestine and these occur at more cephalad levels than in normal persons However patients with other diseases but with normal liver function may have a similar flora without manifesting clinical or biochemical abnormalities and even in cirrhosis the large intestine is the main site of ammonium production The increased blood ammonium levels in cirrhosis must be due not to increased intestinal ammonium production but to decreased ability of the liver to metabolize ammonium or to the presence of a collateral circulation bypassing the liver

Since glucose was found to reduce bacterial NH_4 production the low protein high carbohydrate diet prescribed for patients in hepatic coma may reduce blood ammonium partially by lowering available nitrogenous substrate and partially through the glucose effect Lactobacilli which produce no ammonium are believed to become prominent in the intestinal flora when a milk diet is given Such a diet may be useful in hepatic coma

Antibiotics affecting the principal ammonium producers bacteroides proteus and coliforms should be of value in hepatic coma Chlortetracycline is only partially effective but other wide spectrum antibiotics such as neomycin or a

tions and thus is another expression of the abnormal secretory products of exocrine glands characteristic of cystic fibrosis of the pancreas

In a review of autopsy material 25 of 116 patients (22%) with cystic fibrosis of the pancreas had cirrhosis Clinical features were hepatosplenomegaly, absence of icterus and symptoms of portal hypertension The liver was larger in the earlier stages than later Although only 7 of 325 (2%) patients with cystic fibrosis of the pancreas have developed portal hypertension, this accounted for one half of all the children with symptoms of portal hypertension secondary to hepatic fibrosis

► [If viscid secretions are responsible for the pancreatic and pulmonary changes in this disease it has always been surprising that viscid bile should not cause some damage to the secretory system of the liver Apparently it does —Ed]

In Vitro Production of Ammonium and Amines by Intestinal Bacteria in Relation to Nitrogen Toxicity as Factor in Hepatic Coma is reported by Elizabeth A Phear and B Ruebner[6] (Postgrad Med School London) The organisms were isolated mainly from the feces of patients with hepatic cirrhosis before and after chlortetracycline therapy A few were obtained from ileal contents Ammonium and amine production by the bacteria were studied in mediums containing a mixture of amino acids

Without glucose the various species except lactobacilli produced equal quantities of ammonium in relation to growth The addition of glucose increased growth of all strains but decreased NH_4 production In the presence of glucose, the coliform, proteus and bacteroides strains were the most potent NH_4 producers and gram negative bacteria produced more NH_4 than the gram positive ones Growth and production were unrelated to the initial NH_4 content of the medium Ammonium production was similar in amino acid and casein mediums but much less in a blood digest medium

Most strains possessed no urease activity but Bacterium aerogenes three species of proteus and one strain each of Bact coli and Staphylococcus pyogenes produced more NH_4 after addition of urea to the medium than before Proteus and Bact aerogenes may thus be of clinical significance in cirrhotic patients with elevated blood urea levels

(6) Brit J Exper Path 37 53 262 June 1956

Chlortetracycline in the medium decreased NH_4 production in relation to growth of Bact aerogenes and a hemolytic strain of Streptococcus faecalis It had no effect on Bact coli Bact freundii P morganii P vulgaris P mirabilis and Lactobacillus plantarum and augmented NH_4 production by a microaerophilic streptococcus

Proteus mirabilis produced the most amines and casein was the best medium for amine production by all species Chlortetracycline prevented amine formation by Bact freundii and Bact aerogenes but had little or no effect on hemolytic Str faecalis and P mirabilis

The volume and bacterial content of gut fluid are unknown and in vivo intestinal ammonium production cannot be measured Since in this study bacterial cell nitrogen was of the same magnitude as NH_4 nitrogen produced and since the daily nitrogen content of feces is 1 3 Gm in vivo NH_4 production may be in the order of grams rather than milligrams

Patients with cirrhosis of the liver have increased numbers of coliform bacteria and Str faecalis in the small intestine and these occur at more cephalad levels than in normal persons However patients with other diseases but with normal liver function may have a similar flora without manifesting clinical or biochemical abnormalities and even in cirrhosis the large intestine is the main site of ammonium production The increased blood ammonium levels in cirrhosis must be due not to increased intestinal ammonium production but to decreased ability of the liver to metabolize ammonium or to the presence of a collateral circulation by passing the liver

Since glucose was found to reduce bacterial NH_4 production the low protein high carbohydrate diet prescribed for patients in hepatic coma may reduce blood ammonium partially by lowering available nitrogenous substrate and partially through the glucose effect Lactobacilli which produce no ammonium are believed to become prominent in the intestinal flora when a milk diet is given Such a diet may be useful in hepatic coma

Antibiotics affecting the principal ammonium producers bacteroides proteus and coliforms should be of value in hepatic coma Chlortetracycline is only partially effective but other wide spectrum antibiotics such as neomycin or a

bral oxygen utilization between groups II and III suggests that cerebral function is maintained until low levels of oxygen consumption are reached then additional reduction though slight may produce profound deterioration of function

The depression of cerebral oxygen utilization associated with hepatic insufficiency cannot be attributed to elevated blood ammonia or to increased ammonia uptake by the brain since the decreased cerebral oxygen utilization observed in group II as compared with group I was not associated with increased levels of blood ammonia Also the previously reported high cerebral arteriovenous ammonia difference and increased cerebral uptake of ammonia in patients with hepatic coma was not confirmed In fact the values found in patients in hepatic coma were similar to the cerebral ammonia uptake and arteriovenous difference seen in 10 normal persons It was also apparent that there is no good correlation between the blood ammonia level and the neurologic manifestations of hepatic insufficiency Although ammonia is not excluded as an etiologic agent in the development of hepatic coma it certainly is not the sole responsible factor

The diminished rate of cerebral oxygen utilization in hepatic coma indirectly indicates failure of carbohydrate utilization since the blood glucose levels were normal The accumulation of pyruvate suggests a disturbance of the pyruvic oxidase system Therefore impairment of keto acid oxidation may be partly responsible for the elevated blood ammonia levels since such oxidations provide energy for reductive amination of glutamic acid to form glutamine

Although the brain is responsible for a large part of the total carbohydrate oxidation it is possible that the elevated pyruvate and ammonia seen in hepatic coma may be due entirely to impaired metabolism in other tissues This is especially probable since the brain continues to take up ammonia and pyruvate during hepatic coma However impaired intermediate carbohydrate metabolism prevents as cerebral dysfunction because of the unique obligatory dependence of the brain on carbohydrate oxidation as its important source of energy

Clinical Study of Effect of Arginine on Blood Ammonia
The formation and breakdown of arginine are essential steps

combination of two drugs certainly should be more useful ► [If we believe that amines and ammonia produced by intestinal bacteria play their part in precipitating hepatic coma this is the type of basic information needed. It would also be nice to have some basic information concerning the action of another remedy commonly advocated for hepatic coma i e laxation How does a laxative affect colonic bacterial content diffusion of amines into the blood or loss of fluid and electrolytes into the gut?—Ed]

Cerebral Metabolism in Hepatic Insufficiency is described by Joseph F Fazekas Howard E Ticktin Wilfred R Ehrmantraut and Ralph W Alman[7] (District of Columbia Gen l Hosp) Fifty one patients with advanced cirrhosis were divided into three groups on the basis of neurologic manifestations group I those with no evidence of cerebral dysfunction group II those with lethargy somnolence confusion or both and group III those in hepatic coma Cerebral metabolism was evaluated by measuring cerebral blood flow oxygen content of blood mean arterial pressure blood ammonia and pyruvic acid and by electroencephalograms

In group I significant reduction ($p < 0.5$) below normal values was observed in cerebral blood flow cerebral oxygen utilization (2 3 cc /100 Gm brain/minute normal 3 3) and cerebral arteriovenous oxygen difference Arterial blood ammonia was significantly elevated in 7 of 12 patients Ammonia concentration in cerebral venous blood was the same or slightly lower than arterial blood The cerebral arteriovenous pyruvate difference was normal In group II the findings were similar to those in group I except that cerebral oxygen utilization was more reduced (1 7 cc /100 Gm brain/minute) In group III blood ammonia levels were increased to a higher level and cerebral oxygen utilization (1 6) and mean arterial pressure were reduced

Reduction of cerebral oxygen consumption in patients with advanced hepatic insufficiency but without neurologic disturbance (group I) was unexpected The rate of cerebral oxygen utilization at which cerebral dysfunction becomes detectable has not been determined but would appear to be less than 2 2 cc of O /100 mg brain/minute in patients with hepatic insufficiency Further reduction in cerebral oxygen utilization associated with appearance of mental changes indicates further reduction of cerebral enzymatic activity in groups II and III The lack of significant difference in cere

(7) Am J M d 21 843 849 December 1956

in the liver s conversion of ammonia to urea (Fig 98) Under experimental conditions an artificially elevated blood ammonia level can be lowered and the urea level raised by intravenous administration of arginine These facts prompted John S Najarian and Harold A Harper[8] (Univ of Calif) to study the effects of arginine on 15 patients with liver disease complicated by encephalopathy and elevated blood ammonia

Ammonia levels were determined by the microdiffusion method of Conway within 5 minutes of drawing blood (normal 40 60 µg /100 ml) The therapeutic solution was prepared by adding 25 Gm of L arginine HCl to 400 ml of pyrogen free distilled water and autoclaving for 20 minutes at 15 lb pressure 100 ml of 50% dextrose was added just before use and the total 500 ml amount infused over a 1 2 hour period

The disease states fell into four categories (1) exogenous ammonia intoxication in cirrhosis (1 patient) (2) cirrhosis with either high protein intake or gastrointestinal bleeding (6 patients) (3) vascular shunts around the liver (3 patients) and (4) hepatic insufficiency caused by hepatitis (3 patients) or lymphosarcoma (2 patients) All had cerebral symptoms ranging from confusion and mild disorientation to deep coma Blood ammonia levels were uniformly elevated ranging from 80 to 233 µg /100 ml Shortly after intravenous administration of arginine blood ammonia was lowered in all with levels under 100 µg /100 ml being achieved in 7 This was accompanied by improvement in the mental state and increase in the blood urea level Within a few days of therapy 4 of the patients died of gastrointestinal bleeding or liver failure the remaining 11 appeared to be improving

The concomitant lowering of blood ammonia and raising of blood urea nitrogen was taken as evidence that arginine was effectively promoting the conversion of ammonia to urea by enhancing the action of the urea (Krebs Henseleit) cycle Although such treatment lessens the consequences of ammonia intoxication it has no effect on the liver disease itself

► [The rationale of this treatment impl es that even the sick liver s metabolism can be pepped up by selecting one product from a cyclic sequence of

(8) Am J Med. 21 832 842 Decembe 1956

F g 98 —S quen of ea t n nv l ed format o of u a (Courte y of N jar an J S nd Harpe H A Am. J Med. 21 832 842 December 1956)

ment of hepatic copper is difficult but a modified histochemical method is useful

METHOD —A small piece of liver tissue obtained by needle biopsy is placed in freshly prepared 0 1% solution of rubeanic acid (dithio oxamide) in 70% alcohol After 10 15 minutes sodium acetate crystals sufficient to make 0 2% solution are added Twenty four hours later the tissue is washed in 70% alcohol twice in 1 hour changed to absolute alcohol mounted in paraffin cut in 10-15 μ sections mounted on slides and studied with or without counter staining with 0 1% alcoholic cresyl violet Black stained copper will be seen in plaques on the surface of the nuclei and finely distributed in the cytoplasm The gross appearance of the hepatic fragment may also be striking (Fig 99) but to be sure that the black precipitate



Fig 99 —N dle b psy pec men f om p t ent w th h p t l t la d gen t d l h l d be d l t on d omp d w th l h l fi d ont l (Court y f Ch lm T C t l N w E gl d J M d 6 35 24 F b 7 1957)

is not caused by contamination from the biopsy needle the latter should be rinsed with disodium versenate and distilled water before autoclaving

Because of the simplicity of the blood uric acid determination and because hypouricemia is found only in Wilson s disease and the de Toni Fanconi syndrome measurement of this value is the most useful procedure when Wilson s disease is suspected

► [It has been reported (Proc Soc Exper Biol & Med 88 427 1955) that in 16 patients with Wilson s disease only 1 had a blood uric acid level of above 2 9 mg /100 ml In the patients seen by Chalmers the values are lower but he points out (personal communication) that further study of uric acid levels in Wilson s disease is necessary before the accuracy of the test can be considered established —Ed]

Penicillamine New Oral Therapy for Wilson s Disease The ideal drug for treatment of Wilson s disease according

metabolic products and giving this in excess Rumors from other clinics trying arginine in hepatic coma report (1) rapid improvement (?) improvement only after days and (3) no effect at all —Ed]

Hepatolenticular Degeneration (Wilson s Disease) as Form of Idiopathic Cirrhosis is described by Thomas C Chalmers Frank L Iber and L Lahut Uzman[9] (Walter Reed *Army Inst of Res) in the hope that more cases may be dis*covered in the earlier preneurologic stage of the disease when it may be more susceptible to treatment with 2 3 dimercaptopropanol (BAL) Andre has estimated that in 18% of patients with Wilson s disease hepatic disorders may occur before or may be more prominent than neurologic disease and that 5% may never have neurologic symptoms or signs To document this contention the authors present 5 cases with severe liver disease starting between the ages of 5 and 17

Three patients from one family died in 1 Wilson s disease was eventually recognized by clinical biochemical and autopsy findings but the others died without the disease having been suspected and they are assumed to have had hepatolenticular degeneration because of the familial incidence Two patients from a second family initially presented signs of liver disease but subsequently were shown to have hepatolenticular degeneration on the basis of clinical and biochemical evidence Hence Wilson s disease should be considered in all patients with chronic liver disease not attributable to alcohol or malnutrition suspicion should be heightened if the patient is young or has a sibling with liver disease and the diagnosis can be made with some certainty if a sibling has neurologic as well as hepatic abnormalities

A number of tests are available to confirm the diagnosis of Wilson s disease Examination of 3 consecutive 24 hour urine specimens with the patient on a high protein diet will reveal at least one amino acid nitrogen output above the normal upper limit of 500 mg Excessive amounts of specific peptides and of uric acid are also excreted in the urine Because of the increased renal excretion of uric acid blood uric levels are decreased The abnormalities of copper metabolism in Wilson s disease lead to increased tissue concentrations of the metal decreased serum levels of ceruloplasmin an alpha globulin carrying tightly bound copper and cupruria with 24 hour excretions exceeding 100 μg Chemical measure

(9) New E gl d J M d. 56 235 24 F b 7 1957

ment of hepatic copper is difficult but a modified histochemical method is useful

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F g 99 —N dl b op y pec men f om p t t w th h p tol t l d gen ratio fi d l h l d rubea d sol t on d omp ed w h t h l fixed t L (Court y f Ch lm T C t l N w E gla d J M d 256 35 4 F b 7 1957)

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Penicillamine New Oral Therapy for Wilson s Disease The ideal drug for treatment of Wilson s disease according

to J M Walshe[1] (London) should contain—SH or other chelating groups be effective orally nontoxic suitable for repeated use and readily excreted by the kidney Cysteine and methionine fail to meet these requirements Penicillamine (β β dimethyl cysteine) a degradation product of parenteral penicillin found in the urine of patients with liver injury is stable soluble and excreted by the kidneys This compound and other nontoxic thiols were investigated

The effect of penicillamine on the daily urinary copper excretion was studied in 2 normal subjects and in 6 patients with Wilson s disease All were on a diet containing 800 µg copper daily In the normal subjects given 900 mg penicil

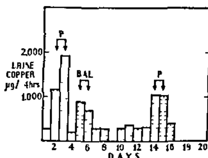


Fig 100—Urinary copp r exc et on n man aged 4 *P* ndicates or l pen cil lamine HCl 300 mg th e t m d y *BAL* 200 mg BAL t am scul rly d ly *asterisk* lost. (Court sy f Walshe J M Am J Med 21 487 495 October 1956)

lamine orally in divided doses for 1 day copper excretion increased from 30 µg to over 600 µg/24 hours Copper excretion in patients with Wilson s disease was 250-430 µg/24 hours before use of the drug Penicillamine in oral doses of 0 5-1 5 Gm daily increased excretion to 1 500 5 000 µg/24 hours (Fig 100) One patient was given 225 mg intravenous penicillamine with an increase in 4 hour excretion from *100 to 1 200 µg* *In contrast intramuscular* BAL raised the excretion in 4 patients to 500 900 µg/24 hours and in 1 to 2 500 µg/24 hours Plasma copper concentration fell from 61 to 44 µg/100 ml after a 2 week course of 0 8-1 5 Gm oral penicillamine daily

Methionine (6 Gm daily) β β β β tetramethyl cystine (900 mg daily) cysteine (500 mg 1 Gm and 2 Gm daily)

(1) Am J Med 21 487-495 Oct ber 1956

cystamine (375 mg) thiourea (1 Gm daily) diethyl dithiol terephthalic acid (1 Gm daily) and dl alanine (12 Gm) were given to patients with Wilson s disease for 1 2 days with no appreciable effect on copper excretion Penicillin which may be degraded to penicillamine did not increase copper excretion

Since both intravenous and oral penicillamine were effective in promoting urinary copper excretion it was not likely that this increase was merely due to greater copper absorption No toxic effects were observed in these short term experiments but it is possible that dimethyl cysteine (i e penicillamine) might cause a metabolic block of cysteine over a long period Although there seems to be no risk in using penicillamine for maintenance therapy of Wilson s disease patients should be followed carefully and a supplement of ethanolamine or choline added to the diet

Evaluation of Four Day ACTH Test in Differential Diagnosis of Jaundice A 4 day course of ACTH gel (40 units every 12 hours) was given to 41 jaundiced patients (18 with acute infectious hepatitis 3 with chronic hepatitis 2 with cholangiolitic hepatitis 8 with cirrhosis and 10 with extra hepatic obstruction) by Thomas C Chalmers Robert J Gill Thomas P Jernigan Floyd A Svec Robert S Jordan Sheldon S Waldstein and Marjorie Knowlton[2] to evaluate this test in the differential diagnosis of jaundice ACTH had been reported to lower bilirubin levels in parenchymal hepatic disease but not in extrahepatic obstruction Response was calculated by expressing the average drop from control levels on the two days following cessation of ACTH as a percentage of the control values

If a 50% drop is defined as a positive test then 65% of the hepatitis patients 12 5% of the cirrhotics and 10% of those with extrahepatic obstruction had positive tests If a 33% drop was considered positive then most of the parenchymal jaundice group had positive tests but so had half of those with mechanical biliary obstruction In 3 cases of extra hepatic obstruction serum bilirubin levels dropped by more than one third without any increase in urinary urobilinogen

Though the mechanism of the ACTH effect on serum bilirubin levels in hepatitis may be the result of its anti

(2) G t oe t rol gy 30 94-899 J 1956

inflammatory action with consequent increased excretion of bile this mechanism does not explain the effect in obstruction especially since no consistent rise in urinary urobilinogen output was detected Perhaps ACTH changes the usual pathways of bilirubin metabolism The test has limited clinical usefulness because the overlap of responses between the groups with parenchymal liver damage and extrahepatic obstruction does not permit accurate diagnosis in the individual patient

► [In a recent report (Gastroenterologia 87 23 1957) one of the early advocates of the ACTH test for the differential diagnosis of jaundice reaffirms his faith in the procedure after studying 18 patients with acute hepatitis and 12 with obstructive jaundice In addition to the sharp drop in icteric index usually observed in his patients with hepatitis the blood prothrombin content tended to rise as ACTH was given Although the author admits an occasional exception the data are not treated statistically The test is also supported on the basis of another case report (Lancet 2 1286 Dec 22 1956) On the other hand there is no doubt that appreciable drops in bilirubinemia have also been observed when ACTH is given to patients with unequivocal extrahepatic obstruction Perhaps it is fair to say that ACTH or a corticosteroid is most apt to have a dramatic effect if bilirubinemia is caused by liver disease but that the test is no more infallible than any of the other procedures used in the differential diagnosis of jaundice —Ed]

Bile Acid Content of Human Serum I Serum Bile Acids in Patients with Hepatic Disease were measured by Daniel Rudman and Forrest E Kendall[3] (Columbia Univ) by improved technics depending on chromatographic separation and spectrophotometric analysis Bile acids were separated into dihydroxy (DBA) and trihydroxy (TBA) types and analyzed for their degree of conjugation with glycine or taurine Urinary measurements were also performed

In 2 healthy volunteers and 8 patients without liver disease no bile acids were detected in the serum or urine In 12 of 13 patients with alcoholic cirrhosis serum DBA was 0 6 5 mg /100 ml TBA was present in only 2 (0 4 and 0 6 mg) DBA was present in the urine of 2 of 8 tested

In 10 patients with obstructive jaundice (3 appeared to have a recognized mechanical extrahepatic cause) serum DBA was 0 5 5 6 mg /100 ml TBA 1 5 14 8 mg TBA exceeded DBA in 8 the ratio of the two acids varying from 0 9 to 4 6 Both types of bile acids were usually found in the urine

In 5 patients with chronic hepatitis without obstruction

(3) J Cl In t 36 530 537 Ap 1, 1957

and 2 with acute hepatitis both acids were found in serum and urine In those with chronic cases serum TBA/DBA ratio was about 0 4 in those with acute 1 2

In 2 patients with obstructive jaundice 35% of the serum TBA was conjugated with taurine 44% with glycine In 3 cirrhotic patients 12 18 and 35% of serum DBA appeared conjugated with glycine and no taurine conjugate was detected

Others have shown that rat liver cells have a hydroxylating system that converts DBA to TBA and a system that conjugates bile acids with taurine and glycine Normally these systems function so as to secrete bile containing a moderate excess of TBA and roughly equivalent amounts of the taurine and glycine conjugates In obstructive jaundice the nature of the serum bile acids reflects this normal partition although the percentage of TBA exceeds that of normal human bile In cirrhosis both enzyme systems are deficient DBA accumulates because it is not hydroxylated and because of decreased conjugation its excretion in bile may be impaired

In acute and chronic hepatitis variable dysfunction of the enzyme systems and intrahepatic obstruction may account for the fact that TBA/DBA ratios lie between values seen in cirrhosis and in obstruction of the biliary tract

► [If the analysis of bile acids can be developed into a practical and accurate procedure we may be provided with a liver function test that really measures liver function —Ed.]

Coagulation Defects in Liver Disease Prothrombin factor V and factor VII are depressed in chronic liver disease and a bad prognosis has attended severe factor V depression in hepatitis To study the hemostatic mechanism in patients with liver disease D C Cowling[4] (Postgrad Med School London) used the Quick time (one stage prothrombin) prothrombin consumption thromboplastin generation and true prothrombin (two stage) test and assayed factor V factor VII antihemophilic globulin and Christmas factor Fibrinogen was not estimated but firm clots were always noted in the Quick one stage test

The Quick time was prolonged in 4 patients with Laennec s cirrhosis largely because of factor V and VII deficiency The Christmas factor was diminished in 2 Thrombo

(4) J Cl P th. 9 347 350 Nov mber 1956

plastin generation was impaired but prothrombin consumption was normal In contrast 2 patients with biliary cirrhosis had normal coagulation factors except for diminished Christmas factor in 1

Factor V was diminished in 2 patients with hepatitis One of these with infectious mononucleosis also showed a prolonged Quick time and diminished factor VII These defects became normal before biochemical or clinical improvement In 2 patients with obstructive jaundice factor VII was lowered and the Quick time was prolonged 1 of these showed factor V deficiency

Coagulation defects in liver disease may result from abnormal protein synthesis or failure of vitamin K absorption which is necessary for synthesis of factor VII prothrombin and possibly Christmas factor synthesis In chronic liver disease with parenchymal dysfunction factors V VII prothrombin and Christmas factor are reduced and it is possible *that Christmas factor deficiency may contribute* to occurrence of hemorrhage Since the decline of antihemophilic globulin does not parallel that of the other factors this factor probably is synthesized elsewhere than in the liver

Deficiencies of coagulation factors were severe only in patients with a prolonged Quick time In contrast bleeding time coagulation time and prothrombin consumption were normal in these patients For practical purposes the Quick one stage test is the most reliable single test for assessing coagulation defects and a markedly prolonged Quick time is a forewarning of possible bleeding Even by assaying each coagulation factor however it is doubtful that precise anticipation of bleeding can be achieved for coagulation factors fluctuate rapidly with the clinical state of the patient

Diagnostic Prognostic and Epidemiologic *Significance of* Serum Glutamic Oxalacetic Transaminase (SGO T) Alterations in Acute Hepatitis was studied by Felix Wroblewski George Jervis and John S LaDue[5] Normal SGO T activity in adults is 22 1±6 8 units It is not increased in infectious neoplastic degenerative reactive allergic or congenital disease unless the liver heart or skeletal muscle is acutely damaged

Toxic hepatitis results in striking elevation of SGO T ac

(5) Ann Int M d 45 782 800 Novembe 1956

tivity which rapidly returns to normal on withdrawal of the hepatotoxin This sequence has been observed in patients with toxic hepatitis from Thorazine® azoserine pyrazinamide cincophen and massive doses of aspirin In 40 patients with infectious hepatitis SGO T activity reached peaks of 400-2 500 units when signs and symptoms were most florid As SGO T level fell the patients improved subjectively and objectively although jaundice did not recede until several days later A similar course was noted in 20 patients with homologous serum hepatitis Hepatitis as a complication of infectious mononucleosis was associated with SGO T levels of 80-300 units When patients with infectious hepatitis become ambulatory small rises in serum SGO T level may occur a rise over 50 units makes return to bed rest advisable

In compensated cirrhosis SGO T level is normal in decompensated or active disease levels vary from 40 to 300 units Levels of 100-300 were observed in patients with extrahepatic obstructive jaundice In 75 of 100 patients with hepatoma or hepatic metastases value of 45 250 were found

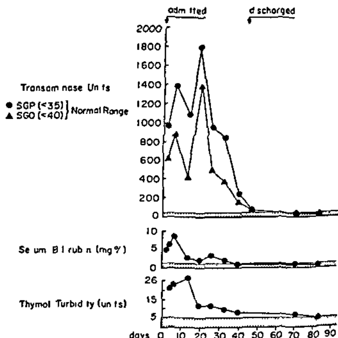
Infectious hepatitis developed in 3 inmates of a cottage housing 154 mental patients After these 3 were hospitalized serial liver function and SGO T tests were performed on the others During the first week 16 had elevated SGO T levels but the rest had normal levels during 3 months of observation In 3 of the 16 symptomatic hepatitis developed 4 remained asymptomatic but had positive thymol tests and SGO T levels over 100 and 9 had no clinical or laboratory abnormality except an SGO T level between 40 and 100 units Thus SGO T determinations permit detection of hepatitis in an asymptomatic or prodromal phase and may be used for this purpose when epidemic spread of infectious hepatitis is a possibility

Serum Glutamic Pyruvic Transaminase (SGP T) in Hepatic Disease Preliminary Report is presented by Felix Wroblewski and John S LaDue[6] (New York) Glutamic pyruvic transaminase (GP T) is an enzyme that is measured by the transamination rate of α ketoglutamate and 1 alanine to glutamate and pyruvate Although its absolute concentration in the liver is less than that of glutamic oxalacetic transaminase (GO T) the relative concentration of GP T and

(6) A I t M d. 45 801-811 Novembe 1956

GO T is higher in the liver than in cardiac or skeletal muscle This fact suggested that SGP T activity might be more specific for liver cell damage than SGO T activity

Mean SGP T activity in serums of 260 normal persons was 16±9 units/ml/minute In absence of liver disease SGP T activity was not increased in infectious neoplastic reactive



F g 101 —V t o n SGP T nd SGO T a t vity i er m b l r b d m thymol t b d ty ea t on e 83 d ys p t ent w th c te h pat t s (Court y of W bl w k F a d LaD J S Ann I t M d 45 801 811 N embe 1956)

degenerative allergic or congenital states In 8 of 9 patients with myocardial infarction SGP T activity was not significantly increased probably because the GP T activity of heart muscle is much less than its GO T activity

Peak SGP T values in 12 patients with infectious hepatitis and 2 with serum hepatitis ranged from 120 to 2 200 and exceeded corresponding SGO T levels (Fig 101) In 3 patients with infectious mononucleosis and hepatic involvement a

similar transaminase pattern was seen but the elevations were less marked The SGP T activities were 300 in a jaundiced patient with carcinoma of the head of the pancreas 279 242 and 164 units in 3 patients with gallstones and 360 in a patient with biliary obstruction due to lymphomatous lymph nodes The SGP T activity which exceeded SGO T activity in all cases fell when the obstruction was surgically relieved Among 15 patients with primary or secondary neoplastic involvement of the liver SGP T activity was increased in 5 SGO T in 12

Although both SGP T and SGO T levels are elevated in liver disease serial alterations in these enzyme levels do not necessarily correlate with liver function tests The SGP T activity appears to be a more sensitive index of acute and SGO T activity of chronic liver disease It has been suggested that transaminase activity in acute hepatic damage results from release of the enzymes from necrotic liver cells but the presence in liver homogenates of considerably more GO T than GP T suggests that the relatively greater increment of SGP T activity in acute liver disease cannot be explained on this basis alone

► [The measurement of serum transaminases as liver tests presents a serious problem in evaluation Doubtlessly these tests as well as countless other enzymatic reactions that could and probably will be used reflect hepatic damage under certain conditions They may therefore be regarded as good test but this is not enough There are already so many methods for evaluating liver disease that a test must be more than good to warrant its routine use Specifically two criteria must be met

1 Does the new test, because of its simplicity or accuracy or both yield information *over* and *above* that already provided by standardized and accepted clinical and laboratory methods? The authors provide little statistical information as to the accuracy of transaminase tests in a series of hepatic disorders and comparison of transaminase measurements and other liver function tests (as for example by the method of Zieve—see 1956-57 YEAR BOOK p 572) is not available In particular it has not been shown that a wide and clearcut difference exists between transaminase levels in jaundiced patients with liver disease and those with a surgically treatable obstruction of the common duct.

As far as good correlation of transaminase levels with clinical phenomena is concerned the availability of the clinical phenomena would seem to exclude the need for a corroborating test In one respect however the transaminase test appeared to yield information not otherwise available mild elevation of the enzyme was the only indication that a group of contacts may have had infectious hepatitis in a nonicteric form.

2 Does the new test measure a specific function which is not measured by other available tests? Since the principle of the transaminase test differs from most available liver function tests (possible exception serum iron determination) it may be supported on these grounds On the other

hand as the authors emphasize themselves it is not certain that the increased serum enzyme levels reflect leakage of the enzyme into the blood from damaged liver cells If this were the only mechanism for elevated *transaminases* in the *blood* why should these levels be elevated in chlorpromazine jaundice in which parenchymal damage is quite restricted (see pages 570 and 572)?

Although this may give the impression of being a philippic on the transaminase test it is not intended as such Rather it is meant as a warning against adoption of this well publicized procedure in the hope that it will solve all diagnostic and prognostic problems related to liver disease As one member of a small clinic plaintively said We are devoting so much money and personnel to doing transaminase tests that routine urines and bloods are harder to get and more inaccurate than ever—Ed]

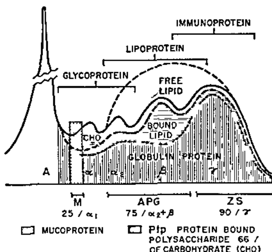
Intraglobulin Fractional Analysis as Aid in Differentiation of Medical from Surgical Jaundice In jaundice hepatocellular function biliary obstruction and tissue response to irritants constitute a triad that determines the distribution of serum globulins Hepatocellular disease increases gamma globulins and if severe decreases alpha and beta fractions Beta globulinemia characterizes chronic biliary obstruction and alpha globulinemia is associated with infections inflammations and neoplasms Although these alterations in serum globulin patterns are detectable by electrophoretic technics practical problems impair the usefulness of these tests Hence Ezra M Greenspan and David A Dreiling[7] (Mount Sinai Hosp New York) recommend a battery of relatively simple test tube procedures to analyze the serum globulin spectrum in jaundiced patients

Mucoprotein (M) is a glycoprotein which in its normal concentration of 40 75 mg/100 ml represents about one fourth of $alpha_1$ globulin Acid precipitable globulin (APG) is separated by a turbidity procedure that isolates 75 90% of alpha plus beta globulins Kunkel s zinc sulfate (ZS) turbidity method measures about 90% of serum gamma globulin A fourth method measures total protein bound polysaccharide (Ptp) which is distributed through all globulin fractions but most heavily in the alpha group (Fig 102)

The M is decreased in *70 88%* of patients with viral hepatitis in 64 80% of cirrhotics and in less than *2%* of those with obstructive jaundice The combination of low M and increased ZS turbidity is common in hepatocellular disorders if a low APG turbidity is also present advanced hepatocellular insufficiency on the basis of postnecrotic or portal cir

(7) Gastroenterology 32 500 509 March 1957

rhosis is likely Normal or high M normal or high APG and normal or low ZS turbidity however constitute a pattern found in 95% of patients with obstructive jaundice and in less than 10% of the initial serums of patients with hepatocellular disease Thus a high APG/ZS ratio argues for surgical jaundice a low ratio for a medical condition The Ptp



Fg 10 —R l t on f 4 s rum gl bul nd to bound ry l ct ph t (Court f G en p E M d D h g D A G t oe t logy 3 500 509 M h 1957)

provides little diagnostic information per se but its high value in myeloma may aid in differentiating the globulin pattern in this disease from that seen in cirrhosis

Since serum globulin patterns are the end result of various and sometimes opposing influences their diagnostic value may be impaired under certain conditions Thus a coexisting inflammatory process may prevent the low M level that would usually characterize an hepatocellular process Since chlorpromazine jaundice is cholestatic and not tissue destroying M/ZS ratios may be normal or high rather than depressed Furthermore decisive alterations in the first few days of a mild hepatitis may be lacking Despite these drawbacks the diagnostic profile afforded by serum globulin par

tition compares favorably with that provided by other liver function tests

► [The complex influences brought to bear on the serum globulin pattern are well illustrated in this review —Ed]

Splenic Artery Aneurysms Gordon J Culver and Herbert S Pirson[8] (Buffalo) *found 213 cases in the literature* and collected 17 radiologically diagnosed cases of their own In autopsies incidence of these lesions is reported as 0 038% with a male female ratio of 1 2 An underlying factor is arteriosclerosis which sometimes involves the splenic artery without affecting other vessels in the body

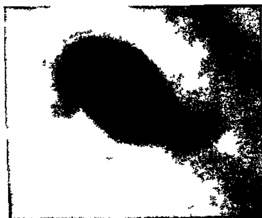
Roentgenologically calcified splenic artery aneurysms appear as oval or round radiopaque densities 1 3 cm in diameter located in the left upper quadrant Usually a continuous or broken ring of calcification is evident with some irregular deposits in the center Occasionally the aneurysms are multiple Gastrointestinal series and intravenous pyelograms permit localization of the ring shadows in an area posterior posteromedial or posterolateral to the stomach above the splenic flexure of the colon and above the upper pole of the left kidney Such localization usually permits differential diagnosis from calcified aneurysm of the renal artery echinococcus cyst and calcified lymph nodes

Six patients all women were operated on 4 for single and 2 for multiple splenic artery aneurysms In none was there a palpable mass but in 1 a thrill and bruit were detectable in the left upper quadrant The symptoms consisted of vague pains and digestive complaints which were relieved by surgery in 2 patients

On the Phrygian Cap William B Ober and Ralph N Wharton[9] (Columbia Univ) review the history of the phrygian cap in headwear and in medicine In 1916 Bartel applied the term to the appearance of a persistent notch in the gallbladder a configuration in which the fundus is bent down to the breaking point a segment of the top appears sharply kinked the bent piece being well turned over like a lappet (Fig 103) Boyden interpreted the phrygian cap deformity as a congenital anomaly It is seen readily on cholecystography and seems to have no pathologic significance

The origin of the cap *is unknown Presumably the Phrygians* migrated to Asia Minor from Thrace in the second mil

(8) Radiology 68 172 3 February 1957
(9) New England J Med 255 571 572 Sept 0 1956.





F g 103 (t p) —Typ l Phrvg n p d f rm t f g llbl d l
F g 104 (b tt m) —B f th B b P rtl i se h w g typ l ncl l p t on f th Ph yg cap
(Cou f Obe W B i Wh rt R N N w E gl d J M d 5 571 572 S pt 2) 19 6)

lennium B C and formed an ill defined agrarian nation The phrygian cap was known to the Greeks as a close fitting conical cap worn by Orientals (Fig 104) and it appeared in late Hellenistic art forms A similar cap was known to the Romans as a *pilleus* and was given a slave on his manumi ion

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(8) Radiology 68 217 223 February 1957
(9) New England J Med 255 571 57 Sept 0 1956

dogs with bilateral or right splanchnicectomy but concomitant vagotomy lessened this effect Passage (perfusion) pressures paralleled resting pressures In control periods food decreased resting and perfusion pressures slightly after right or bilateral splanchnicectomy this response was absent but was partially restored by subsequent vagotomy Choledochal peristaltic activity was variable after surgery except for marked reduction after right splanchnicectomy No clearcut effect on choledochal pressures was produced by cutting autonomic nerve plexuses near the common bile duct

The results show that nerve operations exert little permanent influence on the tonus of the biliary ducts Although nerve operations have been reported to produce acute changes in choledochal pressures such operations are quickly followed by restoration of autonomous nerve function Indications for nerve operations performed for functional disturbances of the biliary ducts are thus rather restricted

► [In view of the recognized tendency of digestive viscera to adjust themselves to extrinsic denervation it is surprising that the bulk of European surgeons enthusiastically recommending autonomic nerve surgery for the relief of various alleged hyper and hypotonias of the biliary tract have been content to accept acute pressure changes recorded during operation as evidence for the effectiveness of the procedure used If the long term results are as unimpressive as indicated by this study from Hungary and by a more limited clinical study (Gastroenterology 15 6 1950) the reluctance of American surgeons to cut sympathetic or parasympathetic nerves to relieve functional biliary tract distress appears more justified than ever —Ed.]

Carcinoma of Major Intrahepatic and Extrahepatic Bile Ducts Exclusive of Papilla of Vater were reviewed by Kamal Kuwayti Archie H Baggenstoss Maurice H Stauffer and James T Priestley (Mayo Clinic and Found) who discovered 63 cases among 24 029 autopsies done from 1915 to 1953 an incidence of 0 26% The anatomic distribution of the lesions—all adenocarcinomas—is shown in Figure 10ɔ Men outnumbered women 2 7 1 and most patients were in the 6th and 7th decades (range 40 81 years)

Presenting symptoms were jaundice (96 8%) weight loss (95%) pruritus (88 5%) anorexia (74%) dark urine (63%) clay colored stools (62%) abdominal pain (57%) weakness (44 5%) fever (14%) diarrhea (13%) and chills (9%) The liver was palpable in 84% of the patients and the gallbladder

(2) Surg Gynec & Obst. 104 357 366 March, 1957

The fate of the phrygian cap in the Dark Ages is obscure but it was resurrected during the French Revolution of *1789 93* as *the bonnet rouge* or *liberty cap* It became a symbol of liberty in the South American states liberated by Simon Bolivar and appears on the official seal and coat-of arms of Argentina Colombia and El Salvador In the United States it appears on the Goddess of Liberty on the dime quarter and half dollar

In the period wherein the nonpathologic nature of the phrygian cap deformity of the gallbladder was debated it may be supposed that its presence on occasion gave the biliary surgeon the license to take the liberty

► [*We speak of a water hammer pulse without ever having held a water hammer and we describe nutmeg livers without ever having seen a nutmeg cut in two The authors have saved us from similar embarrassment with respect to the phrygian cap —Ed*]

Late Effect of Nerve Operations on Tonus of Bile Ducts Experimental Study Nerve operations have been used for *functional disorders of the bile ducts but the physiologic* justification for such procedures is not always clear Z Mester and B Juhasz[1] (Budapest) measured choledochal pressures in dogs by catheters passed into the common duct via a well established cholecystostomy Pressure was recorded by mercury manometer and flow by an electric drop counter Each animal served as its own control after which right or left splanchnicectomy followed by contralateral splanchnicectomy and finally transthoracic vagotomy was done

BEHAVIOR OF RESIDUAL AND PASSAGE PRESSURE AND PERISTALSIS AFTER VARIOUS NERVE OPERATIONS

PROCEDURE	RESIDUAL PRESSURE		PASSAGE PRESSURE	
	Mean value	Variance	Mean val	Variance
Control	18 2	± 4	17 8	± 5 4
Cutting of right splanchnic nerve	15 4	± 3 2	16 4	± 5 0
Cutting of left splanchnic nerve	18 8	± 2 2	18 2	± 3 4
Bilateral splanchnicotomy	15 4	± 2 8	14 2	± 4 0
Bilateral splanchnicotomy and vagotomy	17 2	± 3 4	14 2	± 4 0

Choledochal pressures after each procedure displayed differences smaller than the range of experimental error (table) Average resting pressures were slightly diminished in

(1) Gastroenter l gia 85 281 290 1956

and less than 1 500 Gm in 12 Metastatic or direct spread or both were present in 71 4% Stones occurred in 26 (41 3%) 7 of whom had had cholelithiasis previously treated by surgery In the 6 in whom stones were found in the common duct the stones were all proximal to or at the site of the cancer Whether stones antedated the neoplasms or formed

TABLE 2—CONCENTRATION OF SERUM BILIRUBIN

Lo t f c m	T t l se um b l b mgm p 100 c.c Lou t re d ng	H ghe t re d g	4 e ge	P t ts u th Ser l d t m a t	Fluct t n f j nd ce	Pr g es f j und ce
L ft hepat c d ct	4 1	28 4	17 4	3	3	—
Commo he p t c duct	6 3	53 6	21 5	13	6	7
Cystic d t	8	74 8	3 7	6	5	1
J n t e of cy t c d mmon ducts	7 9	152 7	46 0	7	5	2
Common bile du t	6 6	55 5	24 5	15	7	8
Tot l			27 3	44	26	18

as the result of bile stasis and infection could not be determined and the relation between biliary stones and neoplasm remains unsolved

► [It is generally but not universally accepted that mere obstruction of the common duct without complicating infection or metastatic neoplasm does not cause massive hepatomegaly Another condition must however be added provided a normal gallbladder is present In cancers of the bile ducts as this review shows the lesion may be s tuated high enough to exclude gallbladder function in over half the cases Such cancers may thus explain the occasional case of a really huge liver produced by uncompl cated mechan cal biliary obstruction—Ed]

PANCREAS

Desoxyribonuclease I Activity in Pancreatic Disease was investigated by O D Kowlessar and R K McEvoy[3] (Univ of Rochester) because the depolymerase of desoxyribonucleic acid desoxyribonuclease I (DNase I) is more active in the pancreas than in other body tissues The DNase I activity in

(3) J Cl I t 35 13 5 1330 Dec mb 1956

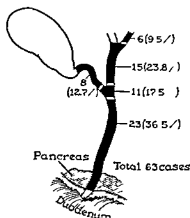


Fig 105—D t but n of e a d g to s te of carc oma b l d cts (Cou tesy f Kuwayt K *et al* Su g Gy ec & Obst 104 357 366 Mar h 1957)

in 31 5% of those who had not had cholecystectomy (Table 1) Serum bilirubin levels and location of the carcinoma were not related and the levels fluctuated by about 20% or more in 60% of the patients (Table 2) Duodenal aspiration per formed in 42 patients yielded bile in 5 and a trace in 14 2 of

TABLE 1—INCIDENCE OF PALPABLE LIVER AND GALLBLADDER

Location of c c noma	*T t l*	*P lp ble l er* (Cases)	*P lpable gallbl dder* (Cases)
Left hepatic duct	6	4	—
Common h patic duct	15	13	3
Cystic duct	8	8	4
Juncture of cystic and common ducts	11	9	2
Common bile duct	23	19	9
Totals No	63	53	18
Per cent		84	31 5*

Ba d n p t t wh h d not h d ch l cyst ctomy

the 42 had definite amounts of blood by this test and 12 a trace The disease was rapidly fatal with hepatic coma the terminal event in 24%

The primary lesion was often small and the proximal ducts dilated Incomplete obstruction was found in 66% and prob ably accounted for fluctuating jaundice and bile in the duo denal contents Among 54 patients in whom the weight of the liver was known it weighed more than 2 000 Gm in 31

stones searched for in 87 by cholecystography or at operation were found in 36 (41% of the 87) Of those with normal gallbladders 37% were alcoholics Alcoholism was present in only 1 with gallstones

Recurrent attacks were noted in 39 rate being 47% in those with gallstones and 43% in those without Pancreatic calcification and pseudocyst formation were found in 16 and 8% respectively of patients with normal gallbladders No pseudocyst developed in those with gallstones and the only patient in this group who showed calcification was an alcoholic Of 30 with gallstones and pancreatitis treated by definite biliary tract surgery only 1 the alcoholic had clear cut recurrent attacks of pancreatitis postoperatively Of 9 with acute pancreatitis but no gallstones treated by cholecystectomy with or without choledochostomy 3 (33%) had recurrences an incidence approximating the natural incidence of recurrence

Incidence of recurrent pancreatitis in patients with or without gallstones is similar but the pattern differs For those with stones and only for those cholecystectomy and choledocostomy are recommended As cholecystography often fails to delineate a normal gallbladder immediately after an attack of acute pancreatitis associated gallbladder disease cannot be diagnosed under such conditions unless nonvisualization of the gallbladder persists for at least a month after the attack of pancreatitis has subsided

► [Although many studies on the course and therapy of pancreatitis have been published most have failed to make the separation necessary to clarify how the precipitating factor—whether biliary tract disease alcoholism trauma or peptic ulcer—affects the natural history of the disease and the results of the specific therapy used Until further separation is achieved along the lines laid out by Kaden and Howard evaluation of the surgical therapy of pancreatitis will remain difficult—Ed]

Pancreatitis Occurring in Heterotopic Pancreatic Tissue
William P Longmire Jr and Manfred A Wallner[5] (Los Angeles) report 2 cases of pancreatitis occurring simultaneously in the pancreas and in aberrant pancreatic tissue

CASE 1 —Man 47 was hospitalized after falling unconscious He had had a large alcoholic intake for 17 years had felt ill for 3 years and had been unemployed for 6 months Nausea vomiting anorexia yellowing skin and low back pain were noted He was dehydrated jaundiced and critically ill The heart sounds were poor and the pulse rate was rapid The abdomen was tense and distended but

(5) S g y 40 412 41 A gu t 1956

the blood was measured by a modification of the method of Allfrey and Mirsky and expressed in micrograms of desoxy pentose phosphorus liberated from the substrate per hour of incubation

The mean DNase I activity in the blood of 32 normal persons was 0 46± 06 μg /ml (range 0 76 1 25 μg) In 25 hospitalized patients similar values were obtained In 23 patients with suspected pancreatitis and serum amylase levels over 200 units (Somogyi) mean DNase I levels were moderately but significantly increased over normal values at the 5% level In contrast marked elevations of DNase I activity to more than 5 times the highest normal value were measured in 10 patients proved at operation or autopsy to have hemorrhagic pancreatitis

Plasma DNase I activity increased in 3 dogs subjected to ligation of the pancreatic ducts The DNase I activity rose steadily but stayed unchanged in 2 control dogs exposed to a sham operation In rats in which pancreatitis was induced by repeated injections of ethionine plasma DNase I activity also increased

The pancreas appears to be active in production and distribution of DNase I The enzyme has been found in canine pancreatic juice but whether it has a specific exocrine function will have to be determined If the pancreas is sufficiently damaged to produce tissue necrosis as it is in hemorrhagic pancreatitis the enzyme is liberated with marked and protracted elevation of DNase I in plasma Measurement of DNase I levels may be useful in diagnosis of pancreatic disease particularly the violent types

► [If further studies should confirm the accuracy and specificity of this procedure it might answer the problem raised by the fact that neither high amylase nor low calcium blood levels can be relied upon to distinguish hemorrhagic pancreatitis and other causes of the desperately acute abdomen (see page 521) —Ed]

Clinical Studies of Natural History of Acute Pancreatitis are reported by Van G Kaden and John M Howard[4] (Houston) To define the natural course of acute pancreatitis 100 surviving patients treated for acute pancreatitis during 1949 54 were followed an average of 3 5 years with 15 followed less than 2 years Diagnosis was usually made on clinical grounds and elevated serum amylase levels Gall

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(4) A M A A h S g 73 69 271 A gu t 1956

and is rarely fatal The hemorrhagic and necrotic type how ever is refractory to therapy and is frequently fatal Four successive deaths from pancreatic necrosis led N C Rogers A O Wilson M J Meynell and W T Cooke[6] (Gen l Hosp Birmingham England) to try anti inflammatory steroids in 6 patients with acute pancreatitis The patients also received standard therapeutic measures

Prednisone 20-25 mg in divided doses was administered daily for 1 week after which dosage was diminished gradually Severely ill patients also received an initial intramuscular dose of hydrocortisone Four patients with moderate to severe edematous pancreatitis improved rapidly 1 within 24 hours but such recovery might have occurred in untreated persons A similar result however was seen in the fifth patient with severe necrotic pancreatitis The sixth a woman aged 36 had severe hemorrhagic pancreatitis observed at laparotomy The surgeon did not think that he would recover and for 24 hours the condition remained grave Thereafter striking recovery occurred Further clinical trial of this treatment in necrotic pancreatitis merits careful consideration

► [This and other reports (Brit M J 2 1524 Dec 29 1956) of individual cases of acute pancreatitis apparently benefited by ACTH or adrenocortical steroids must be read with interest but the treatment applied with caution Not only do the variable course and multiple treatments of acute pancreatitis make it difficult to assess the value of a single therapeutic measure but both experimental animals and man may get pancreatit while receiving adrenocortical agents (1956 57 YEAR BOOK pp 608-9) —Ed]

Chronic Pancreatitis Various etiologic agents have been ascribed but John B Gross and Mandred W Comfort[7] (Mayo Clinic) are impressed with the clinical and pathologic identity of the disease regardless of the precipitating cause Thus chronic relapsing pancreatitis precipitated by alcohol is indistinguishable from that due to other causes When the disease is associated with disorders of the biliary tract it may antedate the biliary disorder rather than vice versa or the association may be coincidental Surgical drainage of the biliary passage moreover may have the same palliative effect in a substantial proportion of cases of chronic pancreatitis without as well as with disease of the biliary tract The association of chronic relapsing pancreatitis with hyperlipe

(6) Lancet 651 652 Sept 29 1956
(7) Am J Med 1 596-617 Oct be 1956

contained no demonstrable fluid The liver was grossly enlarged The red blood cell count was 3 800 000 and the white blood cell count 7 000 urinalysis was negative and prothrombin time 30 seconds (50%) He died 2 days after admission

The liver weighed 3 400 Gm but was not grossly scarred A necrotic hemorrhagic process originating in the region of the pancreas involved the greater omentum mesocolon and root of the mesentery The pancreas was large and firm and contained many areas of fat necrosis and hemorrhage without calculi in the ducts or cysts There was a firm nodule in the tip of a Meckel diverticulum about 40 cm from the ileocecal valve

Microscopically there was severe fatty degeneration in the liver The pancreatic sections showed acute pancreatitis and fat necrosis The nodule in the tip of the diverticulum was composed of pancreatic tissue with acini and ducts containing calculi and revealed an inflammatory process similar to that in the pancreas

CASE 2—Man 33 was first hospitalized in December 1950 with severe abdominal pain nausea vomiting and epigastric and right upper quadrant tenderness Serum amylase was 598 units urinary diastase 13 260 units and serum calcium 10 5 mg /100 ml Diagnosis was acute pancreatitis He responded well to nasogastric suction and sedation and subsequent cholecystograms and a gastrointestinal series were negative

Severe epigastric pain nausea vomiting and diarrhea returned 1 month later and persisted intermittently for 3 weeks An operation was done Feb 16 1951 after diagnosis of recurrent acute pancreatitis

At operation the pancreas was thick and firmer than normal There was slight edema in the retroperitoneal tissues with small patches of fat necrosis A segment of heterotopic pancreatic tissue grossly inflamed in a manner similar to the gland itself was found on the mesenteric border of the jejunum 8 in distal to the ligament of Treitz The jejunal segment containing pancreatic tissue was excised and the tail of the pancreas resected with anastomosis of the proximal cut surface to a Roux Y jejunal limb Despite the continued patency of the anastomosis the operation failed to benefit him

Microscopically both the resected tail of the pancreas and the aberrant pancreatic tissue showed focal fat necrosis interstitial fibrosis and subsiding chronic inflammation

In these 2 patients neither biliary reflux nor any other abnormality of the major pancreatic ducts could have caused the pancreatitis in the aberrant tissue The findings indicate causal factors of a more diffuse nature such as those suggested by Rich and Duff Areas of epithelial metaplasia in the smaller pancreatic ducts were present in both patients

Treatment of Acute Pancreatitis with Cortisone Edematous pancreatitis is the commonest form of acute pancreatitis

rhea and weight loss of 5-40 pounds despite a ravenous appetite Three had steatorrhea and pancreatic calcification 5 had steatorrhea pancreatic calcification and diabetes and 2 had steatorrhea and diabetes One of these 2 was the only patient in the series jaundiced on hospitalization in both diagnosis of pancreatitis was confirmed by operation Appearance of steatorrhea preceded diagnosis of chronic pancreatitis by less than 6 months in 6 of the patients Of the 7 diabetics 4 required insulin and in 3 diabetes preceded steatorrhea by 2 9 years In 3 others diabetes and steatorrhea appeared nearly simultaneously

The striking feature in these 10 patients was absence of typical pancreatic pain although 4 had moderate and atypical upper abdominal distress at various times One had a painless pancreatic cyst Thus chronic and advanced destruction of the pancreas may occur without the usual painful seizures but incidence of such cases among all patients with chronic pancreatitis mu t be low

Surgical exploration was done in 4 as far as is known none had gallstones Two used alcohol heavily Diagnosis can be suspected on the basis of steatorrhea and diabetes and radiologic demonstration of pancreatic calcification is definitive

► [Since pancreatitis can be painless as well as excruciatingly painful is it not reasonable that patients with this disease may complain of inter me liate degrees of pain? Perhaps therefore we hould be more alert to the possibil ty of chronic pancreatitis when patients present a history of atypical upper abdominal pain and normal x ray findings The etiology of the cases presented by Bartholomew and Comfort is puzzling alcohol ism is specifically recorded in 2 but is not mentioned one way or another in the others Since the syndrome described with or without pain is so often related to alcoholism especially when the biliary tract is essentially normal th suspicious reader wonders whether more of the patients had the hal it —Ed]

Effect of Pancreatin on Fat Digestion in an Infant B B Kumar and G E Gibbs[9] (Univ of Nebraska) studied the effect of pancreatin on the fecal fat of an infant with cystic fibrosis of the pancreas proved by sweat test and uncomplicated by pulmonary disease Ten pairs of 3 day fat balance studies were performed with a diet of milk and Pablum During the pancreatin periods Viokase powder (5 Gm /day) was added to the milk During the control periods casein (5 Gm /day) was added as a nonenzymatic protein Mean

(9) A M A J Dis Ch ld. 91 606 607 J e 1956

mia now reported in some 18 cases is also of questionable etiologic significance especially since it is uncertain whether the pancreatitis is the cause or the result of the hyperlipemia

Chronic relapsing pancreatitis may occur in a hereditary form The authors have reported 3 families with definite involvement of 4 3 and 7 members and suspected involvement of 2 2 and 7 members respectively Recently they have encountered other families in which the disease affected 2 or more members The hereditary form of the condition appears to be transmitted as a mendelian autosomal dominant gene and usually begins in childhood Women are affected with this form half again as frequently as men Alcoholism gall stones and hyperlipemia are not etiologic factors The hereditary disease should be suspected when chronic pancreatitis occurs in a child or young adult and the usual predisposing factors are absent

In addition to the well known laboratory features of chronic pancreatitis mild hypochromic anemia may occur leukocytosis is frequent during exacerbations and rarely marked eosinophilia may be seen Slight hyperbilirubinemia is common during the seizures and may persist after the pain disappears Serum transaminase level may be elevated Contrary to the common belief concerning elevated serum enzyme levels in nonpancreatic conditions the authors usually found normal values in renal insufficiency whereas some patients receiving opiates had levels as high as those seen in pancreatitis Analysis of duodenal contents following secretin stimulation may yield equivocal results early in disease when clearcut demonstration of pancreatic insufficiency would be most helpful Provocative serum enzyme tests with secretin and cholinergic drugs with or without morphine have produced such variable results as to limit their diagnostic usefulness Use of the secretin serum enzyme test in 64 patients with various gastrointestinal disorders did not provoke increases of serum amylase increases of serum lipase were observed in only 4 subjects none of whom had unquestioned chronic relapsing pancreatitis

Chronic Pancreatitis without Pain is reported in 10 patients by Lloyd G Bartholomew and Mandred Comfort[8] (Mayo Clinic and Found) Presenting symptoms were diar

(8) Gast oe terol gy 31 727 743 Decembe 1956

METABOLISM

PHILIP K. BONDY M.D.

fecal fat was 58±13% of the ingested fat in control periods and in the 10 pancreatin periods was 33±9% Although there was little change in fecal fat concentration or in consistency of the stools average daily wet weight of the stool decreased from 422 to 274 Gm following pancreatin Thus the calculated increase in fat utilization with pancreatin depended on decreased total weight of the stools

► (For proper substitution therapy of pancreatic insufficiency 24 Gm pancreatin (approximately equivalent to 15% of the normal 24 hour pancreatic output) has been recommended as the daily dose (J A M A 116 2735 1941) Since most pancreatin comes in 5 gr tablets this means 7? tablets a day an amount that may find the sick patient somewhat reluctant Most pancreatin tablets moreover are enteric coated This may protect against gastric pepsin but the protection extends into the small intestine where the very nature of the disease has weakened the digestive capacity of the juices Of a given dose of enteric coated pancreatin tablets consequently one may hope that some will disintegrate in the small bowel one may anticipate that many will reach the cecum intact and one is not surprised—especially if the patient has loose bowels—to find a few in the stool In view of the limited number of tablets that the patient will take and the even smaller number that will be active in the small intestine it is not remarkable that pancreatin has often proved disappointing

Viokase is not perfect It has a taste is fairly expensive and the benefit reported above is modest Yet we have found it much more satisfactory than pancreatin tablets We have tried to give 20 Gm Viokase powder per day either put up in 0 6 Gm gelatin capsules (but this means 11 capsules with each meal!) or by mixing 6 6 Gm in fruit juice or a cola drink—Ed]

PART VI

METABOLISM

THE ADRENAL GLANDS

► ↓It was hoped by many workers that the determination of plasma steroid levels would lead to more direct methods for evaluating adrenal function. This hope has only partly been realized because the concentration of steroids in the plasma which represents the difference between the rate of secretion and the rate of destruction or excretion is not directly or necessarily correlated with the activity of the adrenal gland (See Wallace Christy and Jailer 1956 57 YEAR BOOK p 623) The following papers represent attempts to obtain further information about the factors controlling plasma steroid levels In the first a method is described for estimating the rate of secretion of cortisol (hydrocortisone) The second explains the elevated concentrations of steroids found in the plasma of dying patients known not to have adrenal hyperactivity Both studies emphasize the fact that a single observation of the concentration of steroid in the plasma may be misleading unless the entire clinical picture is taken into consideration —Ed.

Miscible Pool and Turnover Rate of Hydrocortisone in Man were determined by Ralph E Peterson and James B Wyngaarden[1] (Nat l Inst of Health) by serial measurements of the specific activity of circulating hydrocortisone after infusion of trace quantities of 4 C^{14} hydrocortisone

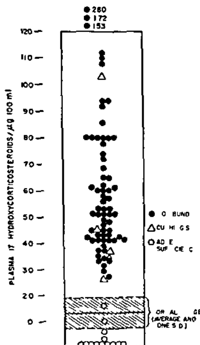
In 13 experiments completed on 9 normal subjects (7 males) aged 16 70 the turnover rate for hydrocortisone varied from 17 to 29 mg /day Suppression of adrenals by prednisone administration significantly reduced the turnover and stimulation of the adrenals by adrenocorticotropin markedly increased it

Diurnal variations in plasma hydrocortisone levels were demonstrated Maximal adrenal activity was during mid morning hours relative stability during the forenoon gradual decline in activity through the afternoon and evening and minimal adrenal activity in the late evening and early morning

Direct measurement of hydrocortisone production has yielded values which confirm estimates based on indirect

(1) J Cl I t 35 55 561 M y 1956

excreted in conjugated form primarily as glucuronides and only a little in the free form This is true also of patients in the terminal state The total amount of 17 hydroxycorticosteroids excreted in the urine is less than that excreted by patients under surgical stress The hydrogenated form tet



F g 106 —Pl m 17 hyd y t co t d l l dy g pat ent omp d w th th se f m l bject p t t w th Cu h g d d those w h ad l ffi en y Th m h d p tent h d l b w th g f th l m (C rt f S dberg A A t l J Cl E doc l 16 1011 1016 A gu t 1956)

rahydrocortisone is cleared from plasma of dying patients at the same rate as from normal subjects

Elevated 17 hydroxycorticosteroid levels in dying patients are due to impaired metabolism of these steroids while they are being produced and secreted by the adrenal cortex at normal or reduced rates Dying is not associated with adre

methods and establishes the general validity of the indirect approach Previous estimates of hydrocortisone production based on urinary excretion of steroids phenylhydrazine chromogenes in urine and renal vein catheterizations yielded an average of 21 mg/day In the direct measurements reported here the projected daily turnover of hydrocortisone averaged 22 mg

This method provides the first direct information on the extent of maximal adrenal response in normal subjects to continuous intravenous administration of adrenocorticotropin After 6 hours of infusion the adrenal response is maximal and hydrocortisone synthesis does not increase during the next 36 hours despite continued administration of adrenocorticotropin After administration of a little prednisone over a short period adrenal hydrocortisone secretion diminishes markedly demonstrating the dependence of the adrenal on pituitary adrenocorticotropin However after this marked and rapid suppression the gland in the normal subject could respond at a normal rate to exogenous adrenocorticotropin given intravenously

Metabolism of Adrenal Steroids in Dying Patients was investigated by Avery A Sandberg Kristen Eik Nes Claude J Migeon and Leo T Samuels (Univ of Utah) by observing the changes in plasma 17 hydroxycortico teroid levels after administration of hydrocortisone and corticotropin

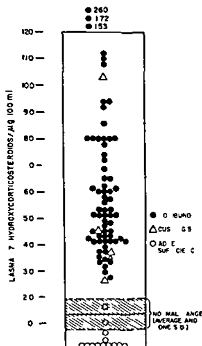
The agonal state was associated with elevated plasma 17 hydroxycorticosteroid levels (Fig 106) These samples of plasma were taken from 72 hours to a few minutes before death Causes of death were the usual illnesses seen in a general ho pital In most of these patients the levels could be further elevated by intravenous infusions of corticotropin

Hydrocortisone administered intravenously was cleared from the plasma of moribund patients much more slowly than in normal subjects Radioactive hydrocorti one (4 C^{14} hydrocortisone) was initially cleared from the plasma at a rate faster than normal but thereafter maintained a plateau (Fig 107) These findings indicate that impaired metabolism of 17 hydroxycorticosteroids is a major factor in the elevated plasma levels in dying patients

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(2) J Cl E d x I 16 1001 1016 A g t 1956

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(2) J Cli Endocr L 16 1001 1016 Aug 1956

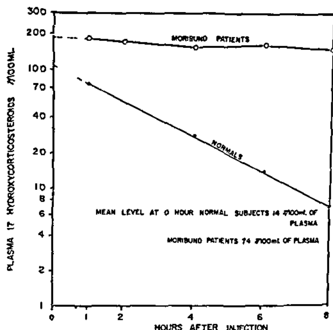
When radioactive corticosterone and cortisol were given to 2 subjects the amount of radioactivity in the chloroform soluble fraction of plasma was twice as great after 4 C^{14} cortisol as after 4 C^{14} corticosterone and the rate of disap pearance of the latter from the plasma was accelerated for the duration of the experiment The amount of radioactivity in the plasma released by beta glucuronidase hydrolysis reached its peak earlier and was of greater magnitude after corticosterone Minimal radioactivity was found in the red blood cells

During the 48 hours following injection 79% of the dose was recovered in the urine

The curves obtained in 2 patients with bile fistulas were similar to those in normal subjects Total activity in the urine after 48 hours was significantly lower than in normal subjects but the sum of biliary and urinary excretion in the bile fistula subjects was greater than 90%

Since the radioactive free steroids disappear from the circulation faster and the glucuronides appear more rapidly after administration of C^{14} corticosterone than after C^{14} cortisol the metabolism of corticosterone in human beings must be significantly more rapid Even though corticosterone is rapidly metabolized the smaller proportion of the con jugated products in the urine indicates that the kidney han dles the conjugated metabolites of corticosterone differently from those of cortisol Decreased excretion of corticosterone metabolites in the urine seems to be associated with increased secretion through the bile apparently the two routes of ex cretion drain the same metabolic pool Even though the lev els of conjugated steroid in the plasma during the initial four hours following 4 C^{14} corticosterone administration were higher than those following 4-C^{14} cortisol the amount of radioactivity excreted in the urine during that time was similar indicating that the conjugates of corticosterone are less readily excreted in the urine than are those of cortisol The reverse was true for biliary excretion

► ↓Study of the regulation of secretion of the adrenal steroids has sug gested that the secretion of aldosterone may be controlled by a mechanism different from that which regulates the secretion of the other cortico steroids The following paper indicates that the secretion of aldosterone



F g 107 —Plasm 17 hydroxy rtic tero d onc ntr t on ft ı ȷ ct on f 50 mg hydrocort one t avenou ly n 12 n rmal d 7 moribu d s bject Lev l sh wn wer obt ı ed by bt acti g le el at 0 ho dott d l e t pol t on t 0 t me (Cou tesy f Sa dberg A A *et l* J Cl n E docr ol 16 1001 1016 August 1956)

nocortical exhaustion in patients who have had no previous adrenocortical insufficiency

► ↓Corticosterone is secreted by the human adrenal in somewhat smaller quantities than is hydrocortisone and its role in human physiology is not clear The following paper indicates that the intermediary metabolism of this steroid is much more rapid than that of cortisol a fact which might influence its effectiveness when comparable doses of the two steroids are compared —Ed

Metabolism of 4 C^{14} Corticosterone in Man was studied by Claude J Migeon Avery A Sandberg A Carl Paul and Leo T Samuels[3] (Univ of Utah) and compared to that of 4 C^{14} cortisol Cortisol is quantitatively the main corticosteroid secreted by the human adrenal it has been isolated from human adrenal vein blood and is present in the peripheral plasma Corticosterone has also been isolated from human adrenal vein blood and is probably present in peripheral plasma

(3) J Cl I' docr l 16 1291 1298 O t ber 195(

the manner in which this control is exerted is unclear ACTH has some effect, as shown by Liddle *et al* in the previous article and also by Muller Riondel and Manning (Helvet. med. acta 23 572 1956) who believe that the effects of ACTH would be more impressive were it not that the increased extracellular fluid volume resulting from ACTH administration reduces aldosterone secretion through another mechanism In any case the fact that hypophysectomy does not cause a fall of urinary aldosterone excretion to subnormal levels and that steroids which suppress the release of ACTH do not suppress aldosterone excretion (viz Venning *et al* J Clin Endocrinol 16 1541 1956) indicates that the pituitary is distinctly of secondary importance in the control of production of this steroid It is of interest that a stress which produced increased aldosterone secretion did not alter the output of other steroids as shown in the next paper —Ed.

Excretion of Urinary Adrenocortical Steroids during Heat Stress Heat has been considered one of many factors which induce stress in the body and elicit increased adrenocortical activity To test this hypothesis K Hellmann K J Collins C H Gray R M Jones J Barbara Lunnon and J S Weiner[5] (Oxford Univ) studied 17 hydroxycorticoid and aldosterone excretion in urine of 32 healthy men subjected to an uncomfortably hot environment

Results showed that any stress resulting from the conditions of heat and work had no significant effect on output of either cortisone and cortisol or of tetrahydrocortisone and tetrahydrocortisol Thorn previously showed that hard physical work has no effect on urinary 17 hydroxycorticoids The present investigation showed that the combination of heat and work was also without effect Therefore it is unlikely that exposure to high temperature alone would significantly affect excretion of adrenocortical steroids This was directly confirmed in the hot chamber

Increased excretion of aldosterone however indicated that exposure to high environmental temperature activated the adrenal cortex to liberate increased salt retaining hormone evidently without mediation of ACTH since output of cortisone and cortisol was unchanged

High temperature produces no change in the output of glucocorticoids in man but in some unknown way leads to increased secretion of the mineralocorticoid aldosterone by the adrenal cortex Thus for the first time involvement of the adrenal cortex in the natural response to high environmental temperatures has been factually shown

► The regulation of the secretion of ACTH is also under study (see 1956 57 YEAR BOOK p 617 and following) The inhibitory effect of re

(5) J F doc ol 14 709 216 N mbe 1956

is less dependent on ACTH than it is on other factors chiefly the sodium intake and extracellular fluid volume (Bartter et al J Clin Invest 35 1299 1306 1956) —Ed

Dual Mechanism Regulating Adrenocortical Function in Man The anterior pituitary gland is known to govern many adrenocortical *functions through the effect of corticotropin* Grant W Liddle Leroy E Duncan Jr and Frederic C Bartter[4] (Nat l Inst of Health) report evidence that secretion of aldosterone and of hydrocortisone by the human adrenal cortex are regulated by different mechanisms

In all subjects tested normal volunteers and patients with hypopituitarism nephrosis cirrhosis amyloidosis and congestive heart failure restriction of sodium intake resulted in increased excretion of aldosterone while excretion of 17 hydroxycorticoids was not influenced and eosinophil count was unchanged *In certain pathologic states* characterized by edema formation 17 hydroxycorticoid output is normal or slightly low while aldosterone output is high even if sodium is not restricted

Administration of ACTH resulted in large increases in 17 hydroxycorticoid excretion and small increases in aldosterone excretion When protracted aldosterone excretion fell to levels below those observed in the pre ACTH periods but corticoid excretion remained elevated Abrupt withdrawal of ACTH after a short course of treatment was followed in each case by fall in urinary aldosterone to low levels and was accompanied by some sodium diuresis

Cortisone 100 mg daily induced adrenocortical atrophy and unresponsiveness but even 200 mg daily did not suppress aldosterone excretion of subjects on low sodium intake The one patient who had typical hypopituitarism showed the characteristic response to ACTH but at no time was there impairment of aldosterone producing mechanism which further confirmed the independence of the hydrocortisone and aldosterone producing mechanisms Aldosterone production does not require stimulation by ACTH and does not depend on an intact pituitary *for its physiologic control*

Apparently secretion of aldosterone responds to change in water and electrolyte metabolism whereas secretion of hydrocortisone is regulated by ACTH

► ↓The secretion of aldosterone is controlled to some extent by the diencephalon (Rauschkolb and Farrell Endocrinology 59 526 1956) but

(4) Am J M d. 1 380 386 Sept mbe 1956

Seven had normal responses before receiving the steroid The poststeroid responses were subnormal resembling the response to corticotropin in patients with adrenocortical insufficiency secondary to hypopituitarism The degree of adrenocortical suppression had no constant relation to the dosage of steroids but duration of administration did play a role

Prednisone in 25 mg doses induced adrenocortical hyporesponsiveness after 7 days of administration whereas four times as much cortisone did not After even relatively short term prednisone treatment 4 days may be insufficient for complete recovery of adrenal responsiveness to corticotropin Adrenal reactivity following longer periods of cortisone therapy is highly variable between patients Evidence suggests that corticotropin therapy after withdrawal of either steroid accelerates the return of adrenocortical response to normal

None of the patients studied objectively showed adrenal insufficiency during or after the periods of steroid withdrawal However the data imply some insufficiency of the pituitary adrenal system For impending trauma such as surgery exogenous steroid should be supplied Administration of corticotropin alone would yield only small transient titers of endogenous adrenocortical hormone

Acquired Resistance to Corticotropins Corticotropin directly stimulates secretion of glucocorticoid hormones from the adrenal cortex Most physicians assume that administration of synthetic corticosteroids is identical with stimulation of the adrenal cortex but this is not justified H F West[7] (Univ of Sheffield) has shown that prolonged administration of corticotropin commonly leads to refractoriness and allergy

A group of 51 patients all with severe rheumatoid arthritis or ankylosing spondylitis were treated continuously with adrenocorticotropin for a month or more while the urine was being analyzed for corticosteroids Initially all responded but 42 patients subsequently acquired resistance to one or more preparations of corticotropin Of these 42 13 were resistant to two preparations 7 to three 3 to four 1 to five and 1 to six different corticotropin preparations After they had acquired resistance to a previous preparation 36

(7) A Rh mat D 15 124 133 J e 1956

serpine in rats (Wells Briggs and Munson Endocrinology 59 571 1956) and of chlorpromazine in man (Christy *et al* J Clin Invest. 36 543 April 1957) suggest that the hypothalamic control centers previously described (1955 56 YEAR BOOK p 605) are probably under control from higher centers in the brain

Suppression of ACTH by exogenous corticosteroids may cause important practical problems The following paper discusses factors influencing the duration of the suppression —Ed

Comparative Effects of Prednisone and Cortisone in Suppressing Response of Adrenal Cortex to Exogenous Adrenocorticotropin Administration of adrenocortical steroids in many diseases is now so widespread that it is essential for the clinician to have a detailed understanding of the physi

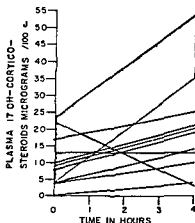


Fig 108 —Effect of prednisone on plasma 17 hydroxycorticosteroid response to infused corticotropin in patients with ... d endocrine ... Limits of normal response ... given by hatched ... Response of patients after prednisone ... shown by solid lines. Many ... corticotropin ... are normal but after ... 17 hydroxycorticosteroid levels ... (Courtesy of Christy N P *et al* J Clin Endocrinol 16 1059 1074 August 1956)

ologic and chemical changes induced An important effect is suppression of endogenous pituitary adrenal function Nicholas P Christy Eleanor Z Wallace and Joseph W Jailer[6] (New York) compared the effects of prednisone and cortisone in suppressing adrenal response to corticotropin measured by plasma 17 hydroxycorticosteroid levels

Figure 108 shows the results of standardized corticotropin tests *in 9 patients who received prednisone—6 in small doses for short periods and 3 in larger doses for longer periods*

(6) J Clin Endocrinol 16 1059 1074 August 1956

common Of 13 patients studied post mortem 6 had had active tuberculosis in the presence of adrenal insufficiency and 5 of these had tuberculosis of the adrenals with active lesions elsewhere Three others had tuberculosis of the adrenals and 5 idiopathic atrophy In at least 2 cases tuberculosis was present elsewhere though the adrenals showed idiopathic atrophy

Of the 31 who had had active tuberculosis at some time 18 had active clinical tuberculosis at the time adrenal insufficiency was pre ent In 5 of these reactivations or spreads of tuberculosis occurred more than a year after diagnosis of adrenal insufficiency was established In 13 clinical tuberculosis antedated or appeared soon after onset of adrenal insufficiency Patients maintained on salt retaining hormone whole adrenal cortical extract or lipoadrenal extract often required significantly more hormone during active tuberculosis Antituberculosis drugs given to 6 patients had little effect on the adrenal insufficiency Of 14 patients who received hormone replacement therapy 3 died each in adrenal crisis Recent dissemination of tuberculosis was found at autopsy in 2

In the presence of adrenal insufficiency active tuberculosis shows the same tendencies to chronicity and relapse as in patients without Addison s disease Hormone replacement is essential There is no evidence that the doses of cortisone required to maintain hormone balance predispose to spread of tuberculosis Antituberculosis therapy should be based on the medical and surgical principles applied to those without coincident adrenal insufficiency

Constitutional symptoms and laboratory findings of both tuberculosis and adrenal insufficiency are often nondescript Patients with Addison s disease and active tuberculosis usually have more severe symptoms tachycardia low grade fever with increased diurnal fluctuation elevated sedimentation rate and leukocytosis with relative lymphopenia In a patient with known adrenal insufficiency these signs and an increased hormonal requirement should suggest active tuberculosis or a similar chronic infection

► [The distinction between physiologic maintenance doses of stero ds for treatmer t of Addison s d sease in a tuberculous patient and inflammation suppress ng doses of the steroids must be kept clearly in mind Although cort sone is dangerous in large doses in physiolog c doses it may be l fe aving for the tuberculous pat ent with adrenal insufficiency—Ed]

patients responded to a subsequent preparation and of these 10 developed resistance to the second After they responded and then acquired resistance to two preparations 8 patients responded to a third

Local reactions at the site of injection occurred in 17 patients usually 1 2 hours later All 51 patients received Acthar® Gel for more than a month and 6 developed local reactions Of 17 patients who received Cortrophin Z® 10 developed local allergic reactions

When resistance was acquired to a particular preparation of corticotropin it was not always accompanied by an intradermal reaction A moderate 2 3 cm delayed reaction to H P Acthar® Gel did not necessarily mean the preparation would be ineffective when administered in adequate dosage The purer the preparations of corticotropin the fewer were the intradermal reactions Patients might have an intradermal reaction to a pork or beef corticotropin yet have no reaction to a more highly purified corticotropin from the same species

Loss of effectiveness of highly purified corticotropin on prolonged administration is due to development of acquired resistance and not as previously surmised to exhaustion of the adrenal cortex The allergen apparently resides in the contaminating or carrier protein Pure adrenocortical hormone will probably prove nonallergenic

Even the highly purified corticotropins are not entirely harmless This may especially be true for patients with permanent or temporary addisonism Efforts should be made to obtain more highly purified corticotropin and preparations of low potency should not be used

Interrelationships between Addison s Disease and Active Tuberculosis Review of 125 Cases of Addison s Disease in which diagnosis of adrenal insufficiency was unequivocal is presented by J P Sanford and C B Favour[8] (Harvard Med School) A history of clinical tuberculosis was elicited from 31 persons 25% including those in whom it antedated onset of adrenal insufficiency and those with active tuberculosis in the presence of the established diagnosis Adrenal calcification was more common than in the tuberculin negative group and a history of familial exposure to tuberculosis was

(8) A I t M d 45 56-7 J ly 1956

assumption The finding in this case of relatively little progesterone in either maternal blood or the placenta itself disagrees with this conclusion Pregnanediol in pregnancy may be the end product of steroids other than progesterone which may or may not be biologically active secreted by either maternal adrenal cortex or placenta in increasing amounts

9 Alpha Fluorohydrocortisone Alone and Combined with Hydrocortisone in Management of Chronic Adrenal Insufficiency Since the advent of cortisone replacement therapy in chronic adrenal insufficiency has improved The acetate form has been used alone combined with NaCl or with various preparations of desoxycorticosterone Patients with Addison s disease have been well maintained on an average of 37 5 mg cortisone daily with 4-6 Gm enteric coated NaCl To improve replacement therapy W Leith and J C Beck[1] (McGill Univ) report experiences with 9 alpha fluorohydrocortisone alone and combined with hydrocortisone in 8 patients observed 12 18 months

Metabolic balance data in 2 patients with Addison s disease showed that 9 alpha fluorohydrocortisone had sodium retaining activity 50 100 times that of cortisone acetate The effect on urinary potassium excretion was not as marked Serum potassium levels decreased but the fall could not be explained by increased urinary potassium excretion No significant effect was observed on nitrogen or vitamin C metabolism when the drug was administered in doses of 1 2 mg daily This increased mineralo corticoid activity and the prolonged action when taken by mouth are ideal qualities for treatment of Addison s disease but its use as sole maintenance therapy was disappointing and it had to be discontinued because of massive edema Excessive fluid retention did not occur at doses of 0 5 mg daily but this was insufficient for adequate maintenance

Excellent replacement results were achieved in chronic adrenal insufficiency using a mixture of 9 alpha fluorohydrocortisone (0 1 mg) and hydrocortisone (5 mg) given twice daily The clinical state was similar to that with cortisone and supplementary NaCl although all the patients had higher blood pressure levels on the newer therapy Serum electrolytes were changed toward normal Development of a

(1) J Cl E doc L 17 280 290 F bruary 1957

Electrolyte and Steroid Metabolism in a Pregnant Addisonian is reported by Irwin H Kaiser[9] (Univ of Minnesota)

Woman 32 delivered her first child uneventfully 9 years previously One year later anorexia amenorrhea bronzing of the skin and weight loss developed Six months later she had an episode of coma collapse and dehydration which responded to emergency treatment maintenance of salt and desoxycorticosterone acetate pellets During the next 5 years minor infections twice precipitated comas Cortisone was begun orally followed promptly by a sense of well being and return of normal menstrual patterns She became pregnant 2 years later

The antepartum course was uneventful After the 28th week thyroid medication was stopped There was definite increase in pubic and leg hair Blood pressure remained stable at 120/80 When labor began she took extra cortisone orally and was delivered spontaneously of a full term infant in excellent condition Cortisone and sodium chloride dosage was resumed on the 1st postpartum day Nine months later during several days of severe heat the patient complained of weakness and anorexia but did not increase salt intake She was found dead in bed one morning At autopsy there was no evidence of tuberculosis The adrenal glands were not found Microscopic examination of the suprarenal fat on each side revealed scarred remnants of one adrenal gland

The clinical course of Addison s disease adequately stabilized by cortisone therapy in the nonpregnant state is not adversely affected by pregnancy and cortisone administration does not disturb the pregnancy The blood hydroxycorticosteroids and urinary hydroxycorticoids were within normal range for pregnancy

The gradual but dramatic reappearance of addisonian symptoms when cortisone was withheld at the 34th week of pregnancy indicates that steroid production by the fetus and placenta were not adequate replacement therapy This was confirmed by the low urinary excretion of corticoids 17 ketosteroids and pregnanediol as pregnancy advanced There is no notable increase in secretion of steroids with adrenocortical activity in pregnancy and findings suggest that increased adrenocortical metabolic demand is not inherent in pregnancy

It has been supposed that the greatly increased urinary pregnanediol excretion in pregnancy is due to metabolism of much greater amounts of progesterone produced in the maternal placental system Vigorous efforts at hormone therapy of abnormalities in pregnancy have rested on this

(9) J Clin Endocrin 16 1251 1261 Sept mber 1956

pressor agents are valuable in the immediate hypotensive episode

Roentgen Therapy in Cushing s Syndrome without Adrenocortical Tumor F C Dohan A Raventos N Boucot and E Rose[3] (Univ of Pennsylvania) present results in 12 patients Various irradiation technics were used Multiple cross firing portals were generally employed Treatment was 5 days a week total duration 11 93 days and total tissue r 600 6 200 to the pituitary region The initial course of therapy produced excellent results in 5 fair in 2 and poor in 5 One patient responded to the fourth course after 3 failed Total dose in the initial course for the 5 who showed excellent response was high (mean 4 350 r) that for the 7 with a poor or fair response was lower (mean 1 339 r) Subsequent therapy was effective in only 1 of these 7

In general 6 months elapsed before marked improvement became manifest in the 5 who had excellent results although they showed appreciable changes in 3 months Of the 7 who showed a fair or poor response 5 have died 1 cannot be traced and 1 still living has hypertension and other signs of adrenocortical hyperactivity All 5 who died had cerebrovascular accidents and in 3 it was the immediate cause of death

It is suggested that Cushing s syndrome will respond to a relatively low total roentgen dose (about 4 000 r) delivered in daily average increments of 100 130 r to the pituitary through portals large enough to include the hypothalamus Before radiation therapy adrenocortical tumor should be excluded by body section films intravenous urography possibly with presacral gas injection hormone assays and determination of the effect of cortisone and hydrocortisone on 17 ketosteroid excretion After irradiation if the disease progresses or remission does not occur in 3 6 months total or subtotal adrenalectomy should be performed

Woman 32 gained 55 lb in 3 years had amenorrhea purple red striation of the skin of the abdomen neck flanks and buttocks purplish discolorations of the face and neck moon face acne mild hirsutism and extreme weakness nervousness and irritability Blood pressure was 170/110 glucose tolerance was impaired She received 3 800 tis ue r to the pituitary gland over 34 days Im

(3) J Cl E doc 1 17 83 J ua y 1957

low serum potassium level in some patients although not accompanied by clinical hypokalemia suggested that the daily requirement of 9 alpha fluorohydrocortisone may be less than 0 2 mg

► [The high potency of fluorohydrocortisone is reflected in the tiny doses needed to maintain electrolyte balance Overdoses may produce severe hypertension which may not appear until after several weeks (Owen Engel and Wester J Clin. Endocrinol 17 272 1957) Owens group also reports angina and edema in overtreated patients Various dosage schedules have been suggested to avoid this difficulty In our clinic 0 1 or 0.2 mg fluorohydrocortisone combined with 25 37 5 mg cortisone has proved satisfactory in most cases On this regimen no salt supplement is needed —Ed]

Acute Adrenal Cortical Insufficiency Precipitation by Infection during Prolonged Cortisone Treatment A case is reported by Robert L Chancey and Alan I Bortz (3415th U S A F Hosp Lowry Air Force Base)

Woman 34 was admitted for shortness of breath and right sided chest pain of 12 hours duration She had had rheumatoid arthritis for 10 years treated for 4 years with cortisone averaging 50 mg daily by mouth On admission she was acutely ill with temperature of 100 F pulse rate 88 respirations 20 and blood pressure 70/40 She was dyspneic and moist rales were heard over the right lung Joint signs of rheumatoid arthritis were present The white blood cell count was 21 000 and a chest x ray showed infiltration in the right midlung She was given penicillin and cortisone 25 mg three times daily

During the night acute vascular collapse developed and she appeared critically ill Blood pressure and peripheral pulses were unobtainable and the heart rate was 150/minute with regular rhythm Heart sounds were distant She was given sodium chloride intravenously levarterenol bitartrate aqueous adrenal extract hydrocortisone and penicillin and was placed in an oxygen tent Her condition remained precarious for 3 days On the 5th day she felt well and took fluid and food by mouth Intravenous medication was discontinued and cortisone was reinstituted orally She was discharged on the 13th day

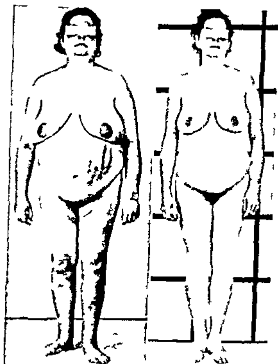
In this case the added stress of pneumonia precipitated acute adrenal insufficiency in the same manner that a crisis develops in adrenal cortical hypofunction if substitution therapy is not increased during periods of stress In patients on long term cortisone treatment every infection should be considered a potentially serious complication cortisone should be increased to compensate for added stress Acute adrenal cortical insufficiency requires immediate replacement therapy with large doses of adrenal cortical hormones Vaso

( ) J A M A 161 523 525 J n 9 1956

the literature) of Cushing s disease in which degree of edema and electrolyte imbalance suggested hypersecretion of adre nal mineral corticoids In the first case secondary to a large chromophobe adenoma excessive aldosterone secretion was not proved because hormone assays could not be made Blood sodium (153 160 mEq /L) and alkaline reserve (CO 30 6 mEq /L) were elevated and chloride (94 mEq /L) was low Potassium level was normal at first but later as the disease progressed pronounced elongation of the Q T complex in the ECG indicated that potassium may have decreased although this was not confirmed by labora tory tests In Doret s patient in whom Cushing s disease was due to a mixed adenocarcinoma (principally basophilic) of the hypophysis hyperaldosteronuria was demonstrated

Man 47 when first signs of pituitary disease developed died 2 years later Hyperactivity of the adrenals was believed secondary to corticotropic hypersecretion of the pituitary tumor since there was regression of biologic signs and slight clinical improvement after partial removal of the malignant adenoma and the first course of radiotherapy Presence of pigmentation also favored a hyper secretion of ACTH or of a melanophore hormone accompanying ACTH

Corticoadrenal hyperfunction was manifested by increased secre tion of glycocorticoids and symptoms of Cushing's disease Increase of 17 ketosteroids was not marked a usual finding in this disease During administration of ACTH 17 ketosteroids formaldehydo genic corticoids and 17 hydroxycorticoids increased showing that the hyperplastic adrenals were capable of increased activity despite their permanent stimulation by endogenous hypersecretion of ACTH Blood sodium level was 156 mEq /L before operation (It decreased immediately after operation and again after radiation therapy to 152 just before death it was 144 mEq /L) Blood potassium level before operation was 3 07 mEq /L The electrolyte disequilibrium and the severe edema aroused suspicion of a hyper secretion of aldosterone confirmed by the finding of 36 4 γ (normal 0-6γ) aldosterone in the urine Although this assay was made when the disease was advanced and congestive cardiac insufficiency may have been a contributory factor several clinical facts indicate that hyperaldosteronism must have been present early in the course of Cushing s disease Edema involving hands and face as well as the legs was one of the first symptoms appearing before hypertension and hyposystole While the edema was accentuated by progression of the disease and cardiac insufficiency its character remained the same i e arms and face remained swollen with gelatinous edema of connective tissue Polyuria and polydipsia were also early symp toms but there never was any sign of sugar diabetes (despite ex cessive hypersecretion of glycocorticoids and significant changes in serum proteins) or of diabetes insipidus since concentration of



F g 109 (l ft) —B fore tr atment.
Fig 110 (ght) —Afte 31 m th f m sta t f x y the apy
(Courtesy of Dohan F C *et al* J Cl Endoc i ol 17 8 32 Ja ry 1957)

provement was rapid (Figs 109 and 110) During the next 5 months she developed symptoms suggestive of Simmond s disease which spontaneously subsided Five years after therapy she was symptomatically well and the result was classified as excellent

► [The program of study and treatment suggested by Dohan is reason able The ability of cortisone or its derivatives to suppress adrenal activ ity has proved to be a poor test of the af ence of tumor We have seen patients with Cushing s disease caused by adrenal hyperplasia whose plasma cortisol concentration failed to rise from its abnormally elevated initial level after intravenous ACTH and we have seen a patient with an adrenal adenoma whose plasma cortisol concentration rose in an ex aggerated fashion after ACTH ACTH suppression tests do not appear to be a reliable criterion for eliminating the possibility of tumor in patients with adrenocortical hyperactivity It is unfortunate that this fact has not yet been generally recognized (e g de Gennes *et al* Presse med. 81 1855 Nov 7 1956) —Ed.]

Hypersecretion of Aldosterone in Cushing s Syndrome and Disease Jean Paul Doret[4] comments on two cases (one from

(4) S ma e hôp P r s 3 921 2928 Sept 30 1956

Case 6—Woman 25 with thyrotoxicosis previously treated with propylthiouracil had relapsed when the drug was discontinued Uptake of I^{131} was 100% BMR +50% and serum protein bound iodine 13 1 µg/100 ml She was given amphenone for 22 days 8 Gm daily for the first three days and then 6 Gm daily Uptake of I^{131} was 23 5% on the 7th day and protein bound iodine was 4 5 µg/100 ml on the 13th day without much clinical change Excretion of 17 ketosteroids remained unchanged and response to corticotropin was unusually great A rash developed on the 15th day of treatment without fever and subsided in 6 days despite continuance of amphenone

Case 8—Woman 35 had carcinoma of the left adrenal gland with pulmonary metastases Urinary 17 ketosteroids varied between 40 and 100 mg/day urinary corticosteroids 12 24 mg/day and serum corticosteroids 24 34 µg/100 ml Corticotropin did not change these levels Amphenone was given in doses of 1 12 Gm daily for 34 days Urinary 17 ketosteroid levels remained the same but urinary corticosteroid levels fell to normal by the 15th day and finally reached levels of 0 3 mg/day Serum corticosteroid concentrations remained unchanged

While she was taking 10 12 Gm amphenone daily she was drowsy and too weak to get out of bed and had nausea vomiting and hypotension Methemoglobinemia was evident Bromsulfalein retention rose from 14 to 23% Thyroid I^{131} uptake fell from 45 2 to 4 3% then rebounded to 82 5% 3 days after treatment was stopped Serum protein bound iodine levels and BMR did not change

Aldosterone Excretion in Healthy Persons Daily and diurnal variations are reported by Eleanor H Venning Inge Dyrenfurth and C J P Giroud[6] (Montreal) The aldosterone was determined by modified assay in adrenalectomized rats Fifty estimations were made on 12 healthy men and 12 on 5 women 12 of the subjects carried on their usual activities during collection of urine In the men average aldosterone excretion was 3 2 µg/24 hours ranging from 0 8 to 6 8 µg In the women average excretion was 3 8 µg/24 hours ranging from 1 7 to 5 5 µg This range for healthy adults is somewhat greater than that previously reported

Eleven healthy persons were followed for 3 8 days range in aldosterone excretion varied from 0 8 to 9 5 µg/24 hours The daily fluctuations were somewhat greater than those observed for corticoid and 17 ketosteroids Diurnal excretion of aldosterone was followed in 9 healthy persons In 6 excretion was higher during the day than at night in the other 3 the trend was inconsistent In persons in whom 17 hydroxycorticosteroid were measured output was consist

(6) J Cl E doc l. 16 13 6 1332 Oct be 1956

urine remained relatively high These findings with changes in the electrolytes correlate well with hyperaldosteronism

Increase of aldosterone secretion in Cushing s disease caused by hypophysial tumor is of great theoretical interest since it supports the hypothesis that secretion of aldosterone is stimulated by ACTH Cancers of the hypophysis are rare and only exceptionally the cause of Cushing s disease All three types of hypophysial cells may be the origin of malig nant adenomas which lead to secondary hyperplasia of the adrenal cortex

► ↓The treatment of hyperadrenocorticism would be much simpler if there were some medical method of restraining adrenal activity compa rable to the action of thiourea derivatives on the thyroid Although no practical method has yet been developed studies such as the following *are paving the way to the development of a useful antiadrenal medication* It is interesting that this drug also reduces thyroid activity Since the need for antithyroid agents is less pressing than that for antiadrenal substances its goitrogenic action is not likely to have important practical implications —Ed

Amphenone Toxicity and Effects on Adrenal and Thyroid Function in Man Roy Hertz James A Pittman and Morris M Graff (Nat l Inst of Health) studied the response to amphenone in 24 patients with cancer adrenal hyperplasia or thyrotoxicosis Toxic side effects observed notably central nervous system depression markedly limit the dosage which usually can be administered Accordingly the pronounced suppression of 17 hydroxycorticosteroid production observed experimentally after amphenone administration can be in duced only irregularly in human beings Of 10 patients stud ied in this regard 7 showed decreased urinary 17 hydroxy corticosteroid excretion and reduced response to exogenous corticotropin A comparable reduction in 17 ketosteroid ex cretion was not observed

In two patients who died of advanced breast carcinoma autopsy revealed the adrenals to be 2 3 times enlarged and histologic changes were comparable to those seen after pro longed corticotropin administration

Amphenone therapy resulted in striking inhibition of thy roid I^{131} uptake in seven of eight patients observed for this effect

The drug is useful for investigation of adrenal function under controlled clinical conditions Its potential for general clinical use is limited by its toxicity

(5) J Cl Endoc n l 16 705 723 J e 1956

inary sodium potassium ratios were depressed Because of the precarious cardiac condition exploratory surgery was delayed further x ray studies were refused by the patient and he died Autopsy revealed the anticipated heart lesions and a well-circumscribed nodule in the left adrenal gland made up of clear polygonal cells Bioassay of an extract revealed a sodium retaining activity of 111 000 γ desoxycorticosterone acetate equivalents/kg tumor tissue

Sodium deprivation and heart failure both operative in this patient are causes of increased urinary aldosterone The excretion level in this patient greatly exceeded that found in the e conditions Secondary aldosteronism due to heart disease is generally associated with frank peripheral edema but edema was minimal and appeared rarely Hypernatremia is generally not seen in cardiac decompensation treated with a low salt diet and diuretics These considerations reinforced the impression that besides possible secondary stimuli for aldosterone secretion a primary hypersecretion must be present This was confirmed at autopsy It should be emphasized that serum electrolytes were less abnormal than those in previously reported cases

Primary Aldosteronism Some Observations on Case in a Cape Colored Woman are reported by L Eales and G C Linder[8] (Univ of Cape Town)

Woman 32 had periodic paralysis tetany and evidence of chronic renal disease proteinuria polyuria and a fixed urinary specific gravity with persistent hypertension Biochemical investigation revealed hypokalemic alkalosis and excessive urine excretion of potassium If supplementary KCL was taken she remained asymptomatic Perirenal insufflation of air revealed a tumor of the left adrenal gland Urine aldosterone varied between 3 and 28 μg /24 hours Plasma levels were cortisol 6 μg aldosterone 0 25 μg /100 ml The tumor was removed and contained 5 600 μg /kg aldosterone Biopsy specimens of both kidneys showed focal ischemic atrophy and attempts at renal tubular regeneration Vacuolar changes in the tubules were slight. Symptoms disappeared after surgery and serum electrolytes became normal

The filtration rate and clearance of endogenous creatinine progressively declined over the 3 years of observation Normal subjects ordinarily excrete less than 15% of the potassium filtered at the glomeruli the amount may rise to 40% with potassium loading In this patient potassium clearance varied between 47 7 and 74 6 ml /minute and the percentage excreted between 35 and 75% After operation potassium clearance fell to 12 1 and 7 9 ml /minute and percentage ex

(8) Quart J M d. 25 539 564 Octobe 1956.

ently higher during the day than at night In most persons there is a diurnal rhythm in aldosterone excretion similar to that observed for corticosteroids and 17 ketosteroids

► [The preceding study extends our knowledge of the normal limits of aldosterone excretion In most of the urinary methods now in use the amount of aldosterone recovered in the urine after administering the steroid to a subject is very small—10% or less of the administered dose. The same reservations must therefore be kept in mind in interpreting urinary aldosterone excretion as in interpreting urinary excretion of other corticosteroids

The syndrome of 'hyperaldosteronism originally described by Conn (1955 56 YEAR BOOK p 612) has excited world wide interest. Since the disease is associated with hypertension it was probably inevitable that ultimately someone would face the problem of differentiating primary hyperaldosteronism (caused by a tumor) from hyperaldosteronism secondary to congestive failure This differential diagnosis is considered in the following paper The fact that rheumatic heart disease was also present is probably only of incidental importance in the differential diagnosis although it was important in causing the patient's death —Ed]

Primary Aldosteronism Report of Case and Discussion of Pathogenesis Outstanding features of this syndrome are hypertension muscle weakness renal and electrolyte abnormalities and increased excretion of a salt retaining hormone in the urine The case reported by Daniel Fine Leonard E Meiselas Jacob Colsky and Sanford Oxenhorn[7] (State Univ of New York New York City) was complicated by rheumatic heart disease The peculiar aspects of this case are considered in detail in relation to genesis of the disturbances that *result from hypersecretion of the adrenal minera*lo corticoids

Man 33 with generalized weakness and dull pain in the left costovertebral angle for 4 years who had had several attacks of rheumatic fever and since age 14 hypertension was hospitalized Examination revealed hypertension cardiomegaly aortic stenosis and insufficiency No masses could be seen by air insufflation and intravenous urography He subsequently had several bouts of left ventricular failure and acute pulmonary edema Persistent hypokalemic alkalosis was then noted serum levels were CO_2 43 5 mEq potassium 2 3 mEq /L A rice diet cortisone and potassium supplements markedly improved symptoms

Hypokalemia hypernatremia and elevated CO level persisted. Urinary potassium excretion was 79 mEq /L despite serum levels of 3.2 mEq /L Bioassay for urinary salt retaining activity revealed values as high as 5500 γ/24 hours expressed as equivalents of desoxycorticosterone Steroid excretion was otherwise normal On a restricted sodium intake and a urinary excretion of 4 mEq /24 hours serum sodium level was 153 mEq /L The urinary and sal

(7) New Engl d J Med. 256 147 152 Jan. 24 1957

delineated by Charles H Slocumb Howard F Polley L Emmerson Ward and Philip S Hench[9] (Mayo Clinic and Found)

Acute hypercortisonism almost always develops during use of large doses of steroids Signs develop quickly and commonly include excessive appetite and weight gain euphoria *insomnia increased nervous tension and irritability* facial rounding increase of fat pads fluid retention edema irregular menses acne and hypertrichosis Acute hypercortisonism should be tolerated only if the disease being treated is so serious that further hormone treatment is imperative or if the treatment period is to be short

Chronic hypercortisonism results from prolonged overdosage with corti one or related preparations even though the overdo age is mild and unsuspected It usually develops insidiously over weeks or months the degree and rate varying with the amount of hormone duration of administration and age and sex of the patient The characteristic feature is cyclic swings of mood and symptoms Increased fatigability muscular and joint aching and emotional instability alternate with periods of stimulation associated with a restless drive and relatively little aching During periods of relative well being the patient is alert co operative and active When depressed he may be unable to concentrate normally and co operation and activity are restricted Spontaneous crying spells occur Successive increases of dosage accentuate the cyclic swings and may complicate the course

These mesenchymal reactions to chronic hypercortisonism must be differentiated from flares of rheumatoid arthriti due to inadequate dosage of steroids or to abuse of previously damaged joints In chronic hypercortisonism synovitis is minim il or not increased A rheumatoid flare affects joints and fibrous tissue but the musculoskeletal symptoms of hypercortisonism are more diffuse and generalized more in muscles than joints and fibrous tissue and are associated with cutaneous and subcutaneous hypersensitivity and hyperalgesia

Test may make the patient with rheumatoid arthritis temporarily worse but benefit the patient with rheumatism and chronic hypercortisonism in whom aching is cyclically re

(9) S I t M d 46 86 101 J y 1957

creted to 19.2%. Pitressin® diminished the urine flow, but increased the specific gravity only to 1.010 and decreased clearance of inulin and para-aminohippurate. Diamox® caused intense paresthesias in the hands and feet and around the mouth, necessitating intravenous administration of potassium.

Ammonia excretion was low for the acid load but high for the urine pH when NH_4Cl was given. The kidneys were able to eliminate acid but only by ammonia production. Apart from the constant loss of potassium, body bases seemed satisfactorily protected.

The periodic attacks of weakness did not last more than a few days and involved the legs and arms without alteration in tendon reflexes. Attacks usually occurred after supplementary potassium was stopped. Recovery was often spontaneous. Tetany with Chvostek's and Trousseau's signs was often observed without hyperventilation and with normal serum calcium level.

The main features encountered in this case were periodic paralysis, tetany and paresthesias, hypertension, polyuria and polydipsia, mild and persistent proteinuria, inability to concentrate urine after deprivation of fluid or administration of Pitressin®, passage of a feebly acid or alkaline urine, excessive renal wastage of potassium with high percentage excretion of filtered load, persistent hypokalemic alkalosis, intermittent hypernatremia, persistent ECG evidence of hypokalemia, demonstration of an adrenal mass by x-ray, increased urinary excretion of aldosterone and abolition of these abnormalities when the tumor was removed.

► [Few cases of hyperaldosteronism have been followed as long and completely as this one. It is of interest that the urinary aldosterone was only slightly elevated and on some occasions was within normal limits. Apparently several determinations of this steroid in the urine are necessary before the possibility of hypersecretion of aldosterone can be discarded. The plasma concentration cannot be interpreted definitely since the normal range is not yet known, but the level observed in this patient is more than twice that found by Simpson and Tait in a large pool of plasma.—Ed.]

Diagnosis, Treatment and Prevention of Chronic Hypercortisonism in Patients with Rheumatoid Arthritis. The term "hypercortisonism" encompasses both the direct and indirect effects of administering cortisone or other related effective adrenocortical hormones or ACTH. The syndrome is

methimazole alone was 4 9 days in 8 of 9 given 300 mg sodium iodide daily after the initial rate was determined the secretion rate slowed markedly (Fig 111) This effect appeared in an average of 1 8 days and reached a maximum in 3 days Average half life during iodide inhibition was 83 3 days None of the patients escaped from the effect of iodide and no difference was detected between patients with and without exophthalmos or between those with diffuse or nod

Fig 111 —Plot f thy ot xi pat ent ec g 30 mg m th m l ev ry 8 h Thy dal d oact ty ount pe min te cted f phy cal dec y plott d on d t Thy d t m lat h rm (thy ot p) plot d t p d y (Co t y f G M A. d D G oot L. J M t bol m 5 682 696 Novembe 1956)

ular goiters One day of treatment with sodium iodide reduced thyroid activity for 3 8 days

When thyrotropin was given during the period when the *secretion rate was maximally slowed by iodide* the rate usually returned to the preiodine rate within 24 hours When iodide was given to patients without thyrotoxicosis the secretion rate was not significantly affected

The experiments show that iodide can inhibit release of hormone from the thyroid gland but how this is accomplished is unknown Iodide inhibited release of hormone in thyrotoxic patients and was related to the level of blood iodide Inhibition could easily be overcome by administering exogenous thyrotropin Response to iodide was not imme

lated to fatigue Physical therapy or salicylates are helpful in patients with a rheumatoid flare up but do not adequately relieve the symptoms of chronic hormonal overdosage Sedimentation rate is of no help in differentiating the two problems

Remarks by the patient that arthritis is getting worse or coming back require careful analysis Detailed observations are needed to permit accurate decision to lower or temporarily raise the dose of hormones

► [The practical importance of this syndrome is obvious It is interesting to compare the symptoms with those often found in potassium deficiency —i e weakness myalgia and emotional instability Although the authors say that the syndrome cannot be prevented by administration of potassium supplements perhaps the amounts they tried were not sufficient to repair the very large potassium deficit which may sometimes occur after prolonged adrenal steroid treatment *In any case it seems worth while to investigate* further the electrolyte balance of these patients —Ed.]

THE THYROID GLAND

► ↓The manner in which iodides reduce the secretion of thyroid hormone in hyperthyroidism has been a subject for argument for many years The following study helps clarify this mechanism —Ed

Effect of Stable Iodide on Thyroid Secretion in Man In the past 3 mechanisms have been postulated for the way in which iodine ameliorates thyrotoxicosis (1) direct action on the thyroid inhibiting the formation or release of hormone and decreasing cellular activity (2) directly inactivating thyrotropin and (3) inhibiting release of thyrotropin from the pituitary Animal experiments have favored the first hypothesis but spontaneous thyrotoxicosis is confined to human beings and extension of the experiments to apply to man is somewhat tenuous To obviate this difficulty Monte A Greer and Leslie J DeGroot[1] studied 15 patients with active thyrotoxicosis 16 euthyroid patients and 1 with moderate postradiothyroidectomy hypothyroidism They measured the half life of thyroid I^{131} as an index of the rate of secretion using methimazole to prevent re entry into the gland of iodide released by breakdown of labeled thyroxin in the body

In the 15 thyrotoxic patients the average half life with

(1) Metabolism 5 682-696 November 1956

Thyroxin does not significantly depress the thyroid in persons who have had hypophysectomy which argues against a direct depressant action on the thyroid gland A fixed dose of thyrotropic hormone was just as effective in elevating thyroid uptake in 1 patient with hypophysectomy whether or not thyroxin had been administered This supports the hypothesis that exogenous thyroid hormone interferes with the output of thyrotropin The critical amount of exogenous thyroid hormone required to inhibit release of thyrotropin varies widely in normal persons

The evidence supported the concept that exogenous thyroid hormone administered to euthyroid subjects induces abrupt cessation of thyrotropin output There was no indication that thyroxin exerts an inhibitory effect on circulating thyrotropin or directly depresses the thyroid gland

Effect of Prednisone and Prednisolone on Thyroid Function with Special Reference to Thyroxin Binding Protein in Nephrosis Max G Sherer and Betty N Siefring[3] (Nat l Inst of Health) studied 14 patients clinically euthyroid hospitalized for various disease states Prednisone treated patients without nephrosis showed a decrease in serum protein bound iodine (PBI) In only 2 of the 8 on whom determinations were made did the level remain unchanged In 4 patients after the maximal drop in the serum PBI level there was a gradual rise but it did not reach the control values during therapy Thyroid 24 hour uptakes of I^{131} determined on 8 patients were decreased in 6 and unchanged in 2 In 1 patient there was a rebound to an uptake higher than the control value when the 24 hour I^{131} uptake was measured 5 days after therapy was stopped

The thyroid secretion rate determined on 1 patient was depressed from a control half life of 5 days to a half life of 8 5 days This returned to the control rate in 12 hours after therapy was stopped

From this study with prednisone and also with prednisolone it appears that these drugs administered to subjects with normal thyroid and renal function consistently induce a fall in the serum PBI level depress thyroid 24 hour I^{131} uptake and retard secretion of thyroid hormone bound I^{131} No consistent change in serum total protein values or basal

(3) J Cl E dx 1 16 643 65 M y 1956

diate but was delayed 1 or 2 days Iodide had no effect on thyroid secretion rate in nonthyrotoxic patients receiving only methimazole in addition but could inhibit the secretion rate of nonthyrotoxic patients receiving exogenous thyrotropin this inhibition could in turn be overcome by administering larger amounts of thyrotropin Thiocyanate had no effect on iodide inhibition

A possible explanation of the data is that thyrotropin and iodide have a mutually antagonistic action on some intrathyroidal mechanism responsible for release of thyroid hormone In part iodide may act by inhibiting release of thyrotropin from the pituitary

► [These observations are confirmed for the most part by Solomon (Metabolism 5 667 1956) Solomon however found that when the rate of thyroxin release was accelerated by exogenous thyroid stimulating hormone in euthyroid subjects the addition of stable iodine resulted in significant slowing of the rate of release This finding seems to contradict Greer and DeGroot Although further study will be needed to clarify this point there seems to be good reason for believing that the effect of iodine in hyperthyroidism is to control the rate of secretion of hormone at the thyroid level rather than to reduce the rate of release of thyroid stimulating hormone or the rate of synthesis of thyroid hormone —Ed]

Inhibition of Thyroidal Radioiodine Uptake Following Intravenous Administration of Thyroxin to Normal and to Hypophysectomized Adult Subjects was studied by Norman E Sharrer and Samuel P Asper Jr[2] (Johns Hopkins Univ)

A single dose of dl thyroxin or l thyroxin intravenously to euthyroid adults depressed accumulation of radioiodine by the thyroid gland In most subjects this appeared within 1 day and became most marked 7 days after injection Diminished thyroidal uptake persisted for 1 or more weeks Serum protein bound iodine became elevated after thyroxin administration but returned to normal within 1 week

This pattern of response was similar to that after hypophysectomy in rats In 2 patients who had had hypophysectomy radioiodine uptake was decreased to the hypothyroid range on the 5th and 6th postoperative days The depression of radioiodine uptake after abrupt administration of thyroxin to euthyroid subjects starts and reaches a maximum as rapidly as it does after hypophysectomy These comparison suggest a common mechanism in both situations—an abrupt cessation of output of thyrotropin

( ) J Clin Endocrin 1 16 1311 13 4 October 1956

with primary myxedema or hypopituitarism No response in TBP was noted in 1 patient with incompetely controlled thyrotoxicosis This patient in contrast to all the others displayed no evidence of estrogenic effects

Administration of diethylstilbestrol did not reproduce completely the alterations in thyroidal economy which occur during normal pregnancy The serum protein bound iodine increased without any change in basal metabolic rate but unlike that in pregnant women the thyroidal uptake of I^{131} was not increased The increased concentration of serum PBI in pregnancy is butanol extractable and presumably therefore thyroxin like material This is assumed to be true also for patients given diethylstilbestrol

The marked augmentation of thyroxin binding by TBP which occurs during pregnancy may at least in part result from the influence of endogenous estrogen The functional consequences of this alteration are unknown

► [It is of interest that Rall and Robbins have calculated from the strength of protein binding and the concentration of protein bound iodine that the amount of unbound thyroxin in the serum is probably normal in pregnant women—i e that the increase in total thyroxin in the plasma just balances the additional circulating TBP —Ed]

Metabolism of Iodotyrosines II Metabolism of Mono and Diiodotyrosine in Certain Patients with Familial Goiter When I^{131} labeled dl diiodotyrosine is injected intravenously into patients with treated myxedema or normal persons labeled iodine appearing in urine is almost entirely inorganic iodide I Monoiodotyrosine is similarly deiodinated but d monoiodotyrosine appears unchanged in urine Normally after ingestion or injection of I^{131} little if any labeled free mono or diiodotyrosine appears in the serum but both have been detected in large amounts in the serum of a patient with hypothyroidism and familial goiter Further studies were conducted by *John B Stanbury J W A Meijer* and *A A H Kassenaar*[5] (Leiden) in 3 patients with hypothyroidism and goiter and in 5 euthyroid relatives of 1 patient

After administration of I^{131} to 2 patient several iodinated components appeared in the urine These included labeled mono and diiodotyrosine and at least two other unidentified components one of which yielded monoiodotyrosine after

(5) J Clin Endocrn 1 16 848 868 July 1956

metabolism could be demonstrated and the serum total cholesterol concentration tended to increase

Prednisone administered to patients with nephrosis did not induce the depression of serum PBI levels noted in normal patients Concurrent with regression of the nephrosis a fall in serum cholesterol level rise in serum total protein level and loss of edema *there was marked rise in the concentration of serum PBI* This occurred despite continued prednisone administration which in patients without nephrosis induced a progressive decrease in serum PBI level

Loss of I^{131} from the gland is due to the loss of I^{131} labeled thyroid hormone Renal loss of I^{131} and changes in iodide space and blood iodide content do not appreciably influence the rate of release of I^{131} The thyroid can respond to thyrotropin even though the secretion rate is depressed *by cortisone*

► [These studies demonstrate that prednisone and prednisolone like cortisone and ACTH suppress thyroid function The effect is apparently not a result of altered renal function The study does not indicate whether the effect is a result of altered function of the thyroid primarily or a secondary effect of alterations of thyroid stimulating hormone secretion or metabolism —Ed]

Effect of Diethylstilbestrol on Binding of Thyroxin in Serum During pregnancy the thyroid becomes hyperplastic radioiodine accumulation by the thyroid is increased and the circulating thyroid hormone is increased These changes are ordinarily associated with the thyrotoxic state but *during* pregnancy there are no symptoms of thyrotoxicity or any increase in basal oxygen consumption beyond that accounted for by the fetus To investigate further this unique dissociation J Thomas Dowling Norbert Freinkel and Sidney H Ingbar[4] gave 30 mg diethylstilbestrol daily to 16 patients including 7 who were apparently euthyroid 4 with primary myxedema 4 with panhypopituitarism and 1 with hyperthyroidism

In each patient who had a normal BMR alterations in thyroxin binding by alpha globulin thyroxin binding protein (TBP) comparable to those occurring during normal pregnancy were induced by diethylstilbestrol This response was not dependent on intact thyroidal or anterior hypophysial function since equivalent degrees of change were induced in postmenopausal women hypogonadal men and patients

(4) J Cl E docr ol 16 1491 1506 N embe 1956

Conversion ratios were unusually high and the quantity of protein bound I^{131} in the plasma at 24 hours seemed to be increased These findings also resemble those of hyperthyroidism and support the hypothesis that in the endemic goiter found in this region there is increased extraction of iodine by the thyroid gland and a faster rate of iodine turnover with synthesis of an adequate quantity of hormonal iodine

► [Similar studies were reported by the same authors (J Clin. Endocrinol 17 99 1957) In this study it was also found that part of the trapped iodine could be flushed from the gland with perchlorate This implies that in iodine deficiency the iodine trap may be more efficient than the synthesis of hormone—rather an unexpected finding —Ed.]

Thyroid Blocking Agent in Etiology of Endemic Goiter According to F W Clements and J W Wishart[7] a significant amount of endemic goiter in certain parts of Australia and possibly elsewhere results from a gastrogenic substance or substances rather than from iodine deficiency

A 1949 survey of school children in Tasmania revealed endemic goiter through most of the island from a low incidence along one coast to high incidence in one half the island Girls were more frequently affected in a ratio of 2 1-6 1 and incidence in both sexes increased with age At least 20% of adult women had goiters This endemic goiter was considered to be due to inadequate dietary intake of iodine Because resistance was anticipated to compulsory use of iodized salt tablets containing 10 mg potassium iodide were distributed to all children under age 16

Another survey 5 years later showed marked increase in incidence of goiter in each age group for both sexes with the exception of girls aged 12 14 and 15 17 years Incidence for each age and both sexes was similar in contrast to the results of the 1949 survey

The fall in incidence among older girls and the general fall in 3 geographic districts confirmed that a significant amount of goiter had been due to iodine deficiency prevented by the tablets of potassium iodide But the failure of complete control led to the hypothesis of a possible antithyroid substance as a cause of part of the endemic goiter in Tasmania A substance 1 5 vinyl 2 thio-oxazolidone had been shown to be present in certain brassicae and cruciferae and by tests with radioactive iodine was found to be an ef

(7) Metabolism 5 6 3 639 November 1956

hydrolysis The major secretion product of these thyroid glands was probably monoiodotyrosine

Intravenously administered dl monoiodotyrosine was excreted in urine unchanged There was no evidence of deiodination In contrast to normal persons the 3 patients excreted little labeled inorganic iodide after injection of l monoiodotyrosine There was however a slight excess of labeled iodide over that in the injection solution Evidently slight deiodination occurred This suggests but does not prove that failure of deiodination itself rather than failure of some metabolic event before it was defective in these patients

Five euthyroid relatives (4 with goiter) of 1 patient with congenital goiter and hypothyroidism were studied after administration of I^{131} dl diiodotyrosine They deiodinated diiodotyrosine but more of the injected dose was excreted unchanged than in another group of 15 euthyroid persons

► [One wonders whether the inability to deiodinate tyrosines and the consequent loss of these iodinated compounds into the urine might produce a sort of iodine deficiency goiter even though the intake of iodine was normal —Ed]

Iodine Metabolism in a Region of Endemic Goiter (Venezuelan Andes) was studied by Marcel Roche Francisco De Venanzi Mario Spinetti Berti Andres Gerardi Jose Mendez Martinez and Jose Forero[6] All subjects were apparently healthy and euthyroid adults with thyroid glands either barely palpable or palpable but not readily visible

Studies with I^{131} indicated a high degree of thyroid efficiency in extracting iodine The 24 hour thyroid I^{131} uptake was not greatly elevated in some cases even normal but the thyroid clearance indicated marked thyroid avidity for iodine

Renal I^{131} excretion was somewhat reduced but clearance was normal indicating that these persons do not develop the ability to conserve iodine through renal mechanisms The 24 hour stable iodine excretion was quite low further confirming the probability that increased avidity for iodine by the thyroid gland in this region is conditioned by iodine deficiency in food and water Saliva radioactivity was generally low corresponding to the values expected in patients with hyperthyroidism who had similar thyroid radioiodine uptake

(6) P oc Soc E per B l & M d 91 661 664 Ap l 1956

to those of purified thyroglobulin derived from thyroid and has an ultracentrifugal sedimentation rate faster than normal serum proteins

In a study of 38 women with Hashimoto s thyroiditis (struma lymphomatosa) this substance was found to resemble thyroglobulin It was demonstrated after administering tracer doses of radioiodine or by standard technics for protein bound iodine This iodinated serum protein was not present in normal controls in measurable amounts and was present in small but significant amounts in serum of a few of 14 patients studied who had granulomatous thyroiditis

In most patients with Hashimoto s thyroiditis if the disease has not yet progressed to complete athyreosis a fraction of iodine can be found which is insoluble in acid butanol This finding is sometimes striking when radioiodine is studied Other butanol insoluble compounds of iodine have been reported after prolonged administration of Lugol s solution or after I^{131} for thyroid carcinoma Whether these three compounds are the same is not known

A combination of normal or increased thyroid uptake of I^{131} normal or decreased values for serum protein bound iodine concentration and decreased BMR—especially if associated with a significant amount of thyroglobulin I^{131} in the serum—may be a guide to diagnosis of Hashimoto s thyroiditis Conversely in acute diffuse thyroiditis I^{131} is usually not taken up by the thyroid gland the BMR is normal or increased serum protein bound iodine value is normal and the sedimentation rate is usually greatly increased

► [This observation is analogous to that of Gribetz Talbot and Crawford (1954-55 YEAR BOOK, p 592) The fact that the abnormal thyroprotein is insoluble in acid butanol (in confirmation of Gribetz) is additional evidence of the practical superiority of the serum butanol-extractable iodine determination as compared with the more commonly used protein bound procedure —Ed.]

Causes of Congenital Myxedema and Genetic Aspect of Thyroid Diseases were investigated by M Bernheim M Berger R Uzan and J Chambron[9] (Lyons) in a study of 49 families of 50 children (2 were sisters) with congenital athyroid myxedema Siblings parents grandparents uncles aunts and cousins on both sides were examined

Death rate during the first months of life was abnormally high among siblings (especially males) of myxedematous

(9) S maine h p P n 32 4104-4113 Dec. 26 1956

fective antithyroid compound The plants must be macerated and stand for a time to allow enzyme action to release the active principle from some precursor Boiling the plant before maceration destroys the enzyme Since all brassicae eaten in Tasmania are cooked, any involved must be so indirectly through another animal which suggested the cow and cow s milk

In 1950 a government free milk plan was started providing one third to one half pint to each child In Tasmania this required greatly increased milk production To keep herds in production through the year farmers had to use additional forage crops and plantings and the feeding of marrow stemmed kale sometimes known as chou moellier (Brassica olenacea meollerii) was increased

The presence of this goitrogen was proved when a substance was found in the milk of chou moellier fed cows which interfered with uptake of I^{131} in humans and experimental animals and resulted in marked hyperplasia of the thyroid in calves of cows fed this forage When chou moellier was fed to rats I^{131} uptake was decreased and thyroid glands became hyperplastic Final proof of the hypothesis that a goitrogenic substance is responsible for a significant amount of endemic goiter requires isolation of the substance from the milk and demonstration of goitrogenic potency in humans

► [In this most important paper it is definitely proved that endemic goiter may in some instances be due to a widely distributed goitrogen Although this possibility has been suspected in the past many authors have suggested that this would merely be a special case of iodine deficiency and that dietary iodine supplementation should be adequate prophylaxis This Clements and Wishart showed to be untrue. In the future study of endemic goitrous regions will have to include measures to rule out the presence of goitrogenic substances The previously mentioned observation by Roche that perchlorate reduced thyroidal iodine in some of his iodine deficiency goiters for example might mean that iodine deficiency is only a partial explanation of the goiters observed in Venezuela —Ed.]

Unusual Iodinated Protein of Serum in Hashimoto s Thyroiditis has been discovered by Charles A Owen Jr and William M McConahey[8] (Mayo Clinic and Found) Protein bound iodine may exist in forms other than thyroxin or inorganic iodide A thyroglobulin has been identified in serum of patients after therapy with radioiodine which is insoluble in butanol has salting out characteristics comparable

(8) J Cl Endocri ol. 16 1570-1579 D ember 1956

to those of purified thyroglobulin derived from thyroid and has an ultracentrifugal sedimentation rate faster than normal serum proteins

In a study of 38 women with Hashimoto s thyroiditis (struma lymphomatosa) this substance was found to resemble thyroglobulin It was demonstrated after administering tracer doses of radioiodine or by standard technics for protein bound iodine This iodinated serum protein was not present in normal controls in measurable amounts and was present in small but significant amounts in serum of a few of 14 patients studied who had granulomatous thyroiditis

In most patients with Hashimoto s thyroiditis if the disease has not yet progressed to complete athyreosis a fraction of iodine can be found which is insoluble in acid butanol This finding is sometimes striking when radioiodine is studied Other butanol insoluble compounds of iodine have been reported after prolonged administration of Lugol s solution or after I^{131} for thyroid carcinoma Whether these three compounds are the same is not known

A combination of normal or increased thyroid uptake of I^{131} normal or decreased values for serum protein bound iodine concentration and decreased BMR—especially if associated with a significant amount of thyroglobulin I^{131} in the serum—may be a guide to diagnosis of Hashimoto s thyroiditis Conversely in acute diffuse thyroiditis I^{131} is usually not taken up by the thyroid gland the BMR is normal or increased serum protein bound iodine value is normal and the sedimentation rate is usually greatly increased

► [This observation is analogous to that of Gribetz Talbot and Crawford (1954-55 YEAR BOOK p 592) The fact that the abnormal thyroprotein is insoluble in acid butanol (in confirmation of Gribetz) is additional evidence of the practical superiority of the serum butanol extractable iodine determination as compared with the more commonly used protein bound procedure—Ed]

Causes of Congenital Myxedema and Genetic Aspect of Thyroid Diseases were investigated by M Bernheim M Berger R Uzan and J Chambron[9] (Lyons) in a study of 49 families of 50 children (2 were sisters) with congenital athyroid myxedema Siblings parents grandparents uncles aunts and cousins on both sides were examined

Death rate during the first months of life was abnormally high among siblings (especially males) of myxedematous

(9) Sem méd h p. Paris 32 4104-4113 Dec 26 1956

infants (14 deaths among 171 children) *Myxedema is more serious in males than in females and may have been a factor in 10 deaths of unknown cause* *Ten of 49 mothers had a history of thyroid disease* Birth of the myxedematous infant was at term in 35 cases 3-4 weeks premature in 4 3-4 weeks prolonged in 7 and probably prolonged about 2 weeks in 4 Average birth weight of myxedematous infants was higher than normal (3 588 ± 107 vs 3 229 ± 35 Gm) No significant influence of number of previous pregnancies or age of the mother was observed

The incidence of a history of simple or exophthalmic goiter was *significantly higher* in families of myxedematous infants (49 ± 7 2%) than in a control group (16 6 ± 2 9%) There were 28 simple goiters 5 exophthalmic goiters and 1 toxic adenoma no infantile or adult myxedema was found *Thyroid disease was found on the paternal side in 8 of the 49 families* *In 5 only the mother was affected* in 5 the mother and other members of the family and in 6 only *other members* *In most cases the history of a thyroid condition was found among aunts and grandmothers on both sides* Siblings and first cousins of myxedematous children showed *no myxedema or other thyroid disease*

Clinically normal parents of myxedematous infant given special tests displayed abnormalities of thyroid function especially increased fixation by the thyroid of radioactive iodine Average fixation in the normal control group at 24 hours was *37 1% ± 2* in 17 fathers and 18 mothers of myxedematous infants it was 54% ±2 2 In 24 siblings of myxedematous patients average iodine fixation at 24 hours was 57 3% ±3 4 Average of protein iodine in blood was slightly more elevated *in parents* (10 µg) and siblings (8 9 µg) of myxedematous infants than in normal subjects (7 6 µg) These metabolic anomalies are identical with those seen in patients with simple goiter

It is concluded that a genetic factor plays *a role in* development of congenital myxedema and that there is a genetic unity for thyroid diseases The mode of transmission appears to be that development of Basedow s disease toxic adenoma simple goiter and congenital myxedema is linked to the presence of an abnormal gene which is the same for various types of thyroid disease Persons with congenital myxedema

are homozygote with respect to the pathologic gene Heterozygotes acquire simple goiter or Basedow s disease or may merely present anomalies of iodine metabolism Apparently congenital myxedema requires the presence of the pathologic gene in the homozygotic state plus a nongenetic factor *such as a reduced placental permeability to maternal* thyroid hormone The authors believe that the pathologic gene augments consumption of thyroid hormone by cells of the organism

► [The existence of familial sporadic goitrous cretinism seems well established It is rather a long jump from this disease where the mechanism of the abnormality is fairly well understood to the general statement that all thyroid disease is genetically linked The possibility of environmental influences must also be considered since these can be familial More studies of the genetic component in thyroid disease are needed — Ed]

Hypothyroid Infant and Child Role of Roentgen Evaluation in Therapy Doses of sodium l thyroxin necessary for normal growth and maturation of the central nervous system and skeleton are significantly larger than those needed only to reverse superficial signs of thyroid privation Lee B Lusted and Donald E Pickering[1] (Univ of California) followed infants and children with hypothyroidism using serial x rays

Retardation of skeletal growth quantitatively approximates duration of thyroid deficiency Retardation persists during inadequate therapy though general clinical response may be good and growth significantly increases Smaller amounts of hormone are required for skeletal growth than for maturation Inadequate therapy during earliest childhood the period of maximal growth potential is responsible for the greatest developmental deficiency in the skeleton

Adequate *treatment* led *to prompt acceleration of skeletal* maturation in all the hypothyroid patients Thyroid privation or inadequate therapy in the congenitally athyroid infant or child during the early critical months of life is associated with mental retardation and delayed skeletal maturation Subsequent adequate therapy can reverse the skeletal stigmas but mental retardation persists Administration of desiccated thyroid or sodium l thyroxin begun early and continued in quantities sufficient to promote immediate and continuing skeletal maturation to normal levels might bet

(1) R d 1 gy 66 708 718 M y 1956

ter supply the otherwise inadequately treated developing central nervous system

Serial x rays of the hands and wrists are valuable guides to therapy in the infant or child with hypothyroidism and increased dosage is indicated when skeletal retardation persists

Boy 3 was diagnosed as a cretin at age 5 months At that time the bone age was that of a newborn infant (Fig 112) After 1 month of therapy with optimal doses of sodium l thyroxin he was



Fig 112 (left) —Cretin aged 5 months with bone age of a newborn infant
Fig 113 (right) —Same patient aged 34 months after 2 years of treatment with sodium l thyroxin Bone age 36 months
(Courtesy of Lusted L B and Pickering D E Radiology 66 708 718 May 1956)

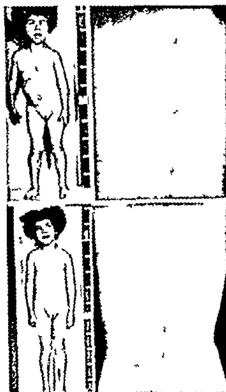
no longer brought to the clinic until age 12 months when therapy was reinstituted and continued for 2 years On this regimen skeletal maturation progressed to normal (Fig 113) although mental retardation persisted

► [Although these changes are of interest, adequate treatment of the hypothyroid infant and child can more conveniently be assured by following the serum protein bound or butanol extractable iodine levels The dose of thyroid needed to maintain these hormone assays at a level which is normal for the child s age is as stated by Lusted and Pickering much higher than the minimum dose which will relieve symptoms —Ed]

Hirsutism in Infantile Thyroid Insufficiency according to J J Ravera J M Cerviño and J C Mussio Fournier[2]

(2) J Clin Endocrinol 16 817 820 June 1956

(Montevideo Uruguay) is most marked on the back and least on the limbs It occurs in both sexes and in ages from the first months of life to adulthood The hirsutism and clinical hypothyrodism both clear with administration of desic



F g 114 (top) —B f t eatment.
F g 115 (bott m) —Afte 12 m th t eatment w th d t d thy d
(Cou t y f Ra x J J s l J Cl n E doc 1 16 837 8 0 Jun 1956)

cated thyroid Three cases of congenital myxederna are reported in which hirsutism was the most interesting clinical feature

Girl 11 was born at term with abundant hair and a heavy growth of lanugo all over the body Symptoms of thyroid insufficiency were present from birth (apathy constipation and delayed mental and physical development) At examination she had the typical appear

ance of infantile myxedema with puffy expressionless facies hoarse voice pot belly and umbilical hernia skeletal age of 4 years dry cold skin and marked growth of hair on the back as far as the sacrum (Fig 114) She was given 0 05 Gm desiccated thyroid every other day The myxedema and hirsutism showed definite progressive improvement (Fig 115)

Disappearance of Bitemporal Hemianopsia Following Correction of Myxedema in Case of Chromophobe Pituitary Tumor is reported by Bengt Skanse and Åke Arén[3] (Univ of

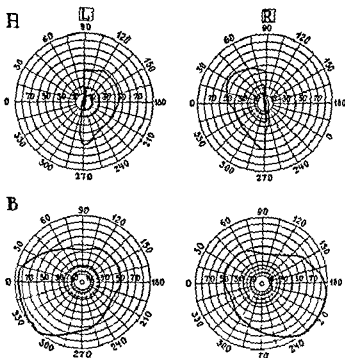


Fig 116 —V l field f p t nt w th h m ph b p t ta y t m C mb d pe m te a d sc e n *Isopte pe ph l 1/333 2/2000 (wh t t t l) t) A be for* ect on of myx d ma V ual acu ty R E 0 7 (+1 5 D ph) L E 0 3 (+1 25 D ph) *B* aft c ecti n f myx dema V sual ty R F 0 9 (+1 5 D ph) L F 0 8 (+1 25 D ph) (Court y f Skan e B and Arén A t doc 1 23 89 294 N mbe 1956)

Lund) Chromophobe pituitary tumors often require surgery or roentgen irradiation and in the presence of secondary glandular deficiencies hormone therapy In most cases treatment is designed to control visual disturbances Indica

(3) A t e doc n 1 23 289 294 N mbe 1956

tions for surgery are rapid progression of visual failure and markedly progressive restriction of the visual fields The trend today is to give preference to irradiation unless the visual field loss is pronounced or visual acuity severely decreased

Whether surgery or irradiation gives best results is still debatable It has been reported that surgery is required less frequently after radiation in doses of 4 000 r when compared with lesser doses

Woman 63 complained of decreased visual acuity For 35 years symptoms of hypothyroidism had progressed insidiously On exam ination she had classic findings of advanced myxedema Optic disks and retinal vessels were normal Visual fields revealed bitemporal hemianopsia (Fig 116) which remained constant during 2 months of observation Skull x rays revealed an enlarged sella turcica Lab oratory examinations confirmed the presence of secondary hypo thyroidism and hypoadrenalism

Irradiation or surgery was refused and she was started on cor tisone and thyroid extract therapy Symptoms of myxedema gradu ally disappeared and visual acuity gradually improved After 14 months of therapy although the sella turcica remained the same visual fields were normal (Fig 116)

Observations on this patient indicate that symptoms of decreased visual acuity in patients with pituitary tumors need not be caused by direct pressure of the tumor against the optical pathways Severe pituitary myxedema should probably be corrected before surgical treatment of chromo phobe tumors is considered The effect of roentgen irradiation or surgery on visual acuity and on visual fields should be judged with caution in patients receiving thyroid therapy

► ↓One of the most active areas of thyroid research in the past years has concerned itself with the intermediate products of the breakdown of thy roxin and the relative activity of the various thyroxin analogues Data regarding the action of triiodothyronine have been presented in previous YEAR BOOKS (1954 55 pp 571 ff 1955 56 pp 591 ff 1956 57 p 641) The following paper reports studies of compounds in which the acid side chain is not the three carbon amino ac d alanine as in thyroxin and tri iodothyronine but the two carbon nitrogen free substance acetic acid — Ed.

Physiologic Activity of Triiodo and Tetraiodothyroacet ic Acid in Human Myxedema was studied in 8 patients by Jacob Lerman and Rosalind Pitt Rivers[4] (Massachusetts Gen l Hosp) Analogues of thyroxin which have substitu tions in the alanine side chain act qualitatively like thyroxin or triiodothyronine but are quantitatively weaker

(4) J Cl E doc 1 16 14 0 1479 N mbe 1956

Tetraiodothyroacetic acid intravenously has one fifteenth the activity of l thyroxin in raising the BMR of patients with myxedema In adequate dosage triiodothyroacetic acid has one fourth to one sixth the activity of thyroxin

Triiodothyroacetic acid in dosages under 1 5 mg daily induces a dissociation of response in myxedema The BMR changes little but there is the expected drop in blood cholesterol level an increase in urinary excretion of creatine return of the ECG pattern to normal appreciable loss of weight and improvement in the myxedematous appearance Large daily doses of the acetic acid derivatives act like thyroxin in that they have a cumulative effect on the basal metabolism

These findings in myxedema substantiate previous reports Administration of triiodothyroacetic acid or tetraiodothyroacetic acid results in an appreciable rise in the BMR during the first few hours which tends to subside in 24 hours Thyroxin in contrast elicits little or no response during the first 24 hours This favors the concept that the acetic acid analogues are the form in which thyroid hormone acts in the tissues

Further degradation of the alanine side chain is apparently not important in the action of thyroid hormone The formic acid derivative of triiodothyronine a loss of one carbon atom beyond the acetic acid derivative of triiodothyronine is inactive in human myxedema in dosage up to 20 mg daily

► [The fact that this group of substances reduces plasma cholesterol and thyroid activity without much alteration of metabolic rate is of great theoretical importance One might wonder about the possible application of this dissociation to the control of plasma cholesterol in situations not associated with thyroid insufficiency Trotter (Lancet I 885 June 9 1956) reports that the hypercholesteremia of 3 euthyroid subjects with coronary disease was in fact lowered by triiodothyroacetic acid without altering the BMR In myxedematous patients his results were like those of Lerman and Pitt Rivers —Ed]

Effects of 3 5 3 l Triiodothyronine in Patients with Metabolic Insufficiency Preliminary Report Decreased thyroid function is known to be associated with generalized depression of metabolism However metabolic depression can occur *in patients who apparently have normal thyroid function* Such patients show symptoms and physical signs that mimic hypothyroidism and have a low normal or subnormal BMR but show normal protein bound iodine levels I^{131} uptake

and cholesterol levels A small proportion have hypopitui tarism nephrosis malnutrition hypogonadism adrenal cortical hypofunction or some other discernible disorder but the rest have a specific disorder metabolic insufficiency or hypometabolism Such patients generally do not improve on thyroid extract thyroglobulin or thyroxin but respond to l triiodothyronine

C Robert Tittle[5] (Univ of Pennsylvania) demonstrated the effects of 3 5 3 1 triiodothyronine in 8 patients with metabolic insufficiency Despite treatment with desiccated thyroid for 6 months to 5 years each of the patients had symptomatic and physical abnormalities due to metabolic depression Basal metabolic rates ranged from —28 to —36% but other thyroid function tests were normal

l Triiodothyronine was administered in increasing dosages to a maximum of 50 100 µg daily Within 1 2 months symptoms of chronic fatigue and aching in muscles and joints disappeared in 6 of the 8 patients Weight bowel function thermal regulation and the BMR improved Two patients with marked sensitivity to desiccated thyroid developed insomnia increased nervousness and palpitations while taking 50 µg daily of l triiodothyronine The effects of overstimulation disappeared within several days when the drug was withdrawn Two others taking 75 µg daily showed mild signs of over stimulation but therapy was not discontinued The other 4 patients tolerated the drug satisfactorily

It was concluded that l triiodothyronine is a rapid and effective metabolic stimulant and therapeutic agent for treating metabolic insufficiency Further studies were warranted

► [This paper and one by Fields (J A M A 163 817 Mar 9 1957) confirm the results previously reported by Freedberg Kurland and Hamolsky (1956 57 YEAR BOOK p 656) In my own personal experience I have not seen such a case although I have looked for one Although the theoretical basis for postulating such a disease seems reasonable and Tittle s and Freedberg s observations are well documented I must confess to considerable skepticism for the moment —Ed.]

Operative Treatment of Thyrotoxicosis Follow up Results in 434 Cases after Four to Seven Years are reported by A Thoren and Hj Wijnbladh[6] (Stockholm) During the period studied surgery was standard treatment Most patients received iodine premedication others thio compounds

(5) J A M A 16 271 274 S pt. 22 1956
(6) A ta docri L 22 224-245 1956

plus iodine Indications for thio compounds alone were recurrences without tracheal compression and with small goiters small goiters with low toxicity exceptionally severe complicating diseases and mild thyrotoxicosis due to a transient causal factor Thio compounds alone were advised only when the complicating disease reduced the expected survival time to a very short period

Among 434 patients there was 1 surgical death and 13 deaths subsequently No patient developed postoperative thyrotoxic crisis The primary mortality was thus 0 2% Tetany developed in 14 patients but persisted in only 6 1 4%) Postoperative vocal cord paralysis was noted in 41 patients but permanent paralysis in only 11 (2 6%)

Hyperthyroidism recurred in 17 patients (3 9%) and 5 (1 2%) had hypothyroidism at follow up Almost 60% 259 patients were euthyroid and entirely comfortable at follow up 62 (15%) were euthyroid with residual symptoms and 43 (10%) were euthyroid in the presence of other diseases

In a survey of 23 reports from the literature the mortality has varied from none to 8% tetany from 0 2 to 3% recurrences from 1 8 to 11 4% vocal cord paralysis from 0 3 to 15 9% and hypothyroidism from 3 7 to 26%

The primary mortality in medicosurgical treatment of thyrotoxicosis can be kept low It should be possible wholly to eliminate the risk of postoperative crisis and metabolic risks in surgical treatment can almost invariably be overcome by careful preoperative treatment

Application and development of various therapies cannot rest solely on statistical reports Each patient should be regarded as a special therapeutic problem Choice of therapy must be influenced by the experience and knowledge of the physician and the available resources

Late Results of Surgical Treatment for Thyrotoxicosis During 1926 39 379 patients with thyrotoxicosis had subtotal bilateral thyroidectomy 75% of the operations were done by one surgeon Follow up of 297 patients 15 28 years after surgery is reported by Stig Borgstrom[7] (Lund Sweden)

Primary operative mortality was 3 7% Age at operation was 15-69 years most patients were aged 30 39 In two thirds preoperative BMR was between 31 and 70% The

(7) Acta chir scand 111 351 369 1956

BMR was determined in 150 patients on follow up and was between −10 and +20% in 75% lower in 13% and higher in 12% Eleven patients had received thyroid therapy for hypo thyroidism continuously for 6 20 years Recurrent hyperthy roidism was diagnosed in 14 patients and was detected on follow up in 3 Late onset of hypo and hyperthyroidism in these patients stressed the importance of long observation before assessing results of surgical treatment for toxic goiter

After discharge 17 patients (6%) required treatment for postoperative tetany 12 continued to require treatment 15 years after surgery 3 have had operation for cataract of both eyes Postoperative vocal changes or recurrent laryn geal palsy were reported by 32% Subjectively 53% of pa tients reported themselves well and 26% almost well Those who did not consider themselves well complained chiefly of nervousness anxiety or cardiac symptoms The present series included a high proportion of emotionally unstable patients and patients with hypertension

Compared with the general population of Sweden mor tality among patients operated on for thyrotoxicosis was higher This is not apparent until 5 years after surgery Age of the patient at operation was apparently unrelated to the excessive mortality These results applied only to women since there were but 35 men in the series a number too small for statistical analysis A relation was seen between excessive mortality from circulatory disease and preceding thyrotoxicosis This ran from toxic goiter which produced brain damage through emotional instability with resulting hypertension to excessive mortality from cardiovascular disease

Thyrotoxic patients even those whose surgery was free of complications should be observed throughout life for signs of hypo and hyperthyroidism and changes in emo tional and cardiovascular states

Thyrotoxicosis as Cause of Cerebral Dysrhythmia and Convulsive Seizures In thyrotoxicosis a number of symp toms involve the central nervous system and such gross neurologic disturbances as coma bulbar palsies and athetot ic and choreiform movements have occurred It is not sur prising that electroencephalographic abnormalities have

been recorded Bengt Skanse and G Eberhard Nyman[8] (Univ of Lund) systematically studied 44 patients who had thyrotoxicosis for evidences of EEG abnormalities before and after treatment

Electroencephalographic changes were common definitely abnormal EEG was found in 43% of the cases and borderline abnormalities in 25% None of the patients had had EEG's before thryotoxicosis had appeared so that comparisons could not be made In 4 the abnormalities were focal and in 1 the focal changes were recorded at the time of a major seizure

When the thyrotoxicosis was ameliorated, the abnormalities regressed in 16 of the 19 patients who had definitely abnormal tracings and in 4 of the 11 with initial borderline tracings The abnormalities were not related to severity or duration of the disease or to the systolic blood pressure They may have been more frequent in older age groups

The type and severity of the EEG changes varied widely from patient to patient Whether the disorder is sometimes primary in the brain or always secondary to the disturbed metabolism of thyrotoxicosis could not be determined There is no doubt that thyrotoxicosis can produce central nervous system disturbances and may precipitate pre existing central nervous system disorders Clinically the problem is to determine to what extent each contributes

Although thyrotoxicosis can cause major convulsive seizures only rarely it should be considered in differential diagnosis

Clinical Appraisal of Radioiodine Tests of Thyroid Function was made by William M McConahey Charles A Owen Jr and F Raymond Keating Jr[9] (Mayo Clinic and Found) to evaluate simultaneously the relative merits of 7 practicable diagnostic radioiodine procedures in the same patients Tests used were (1) 6-hour uptake (2) 24-hour uptake (3) 24 hour excretion (4) accumulation rate (5) extrarenal disposal rate (6) conversion ratio and (7) thyroidal iodide clearance Tracer doses of radioiodine were given to 92 patients with exophthalmic goiter 46 with adenomatous goiter without hyperthyroidism 19 with adenomatous goiter and hyperthyroidism 13 with myxedema 181 clinically normal

(8) Acta endocrinol. 22 246-263 July, 1956
(9) J Clin Endocrinol. 16 724-734 June 1956

with respect to the thyroid and 38 initially suspected of hav ing exophthalmic goiter but later judged to be euthryoid

A tracer dose of radioiodine was given intravenously at 8 a m and continuous in vivo readings were taken for 35 minutes over the thyroid with a scintillation counter The thyroidal iodine clearance was then calculated Six hours and 24 hours after administration of radioiodine single readings were taken over the thyroid to determine the proportion of the dose in the gland Patients were provided with 6 bottles for collection of urine at 2 4 6 12 18 and 24 hours after radio iodine administration From data on urinary excretion of ra dioiodine extrarenal disposal rate was calculated and from data on both urinary excretion and in vivo collection of radio iodine thyroidal accumulation rate was calculated Twenty four hours after administration of the tracer venous blood was drawn and the ratio of protein bound radioiodine in the serum to total radioiodine in the serum was determined The normal range of values for each test studied was estimated *graphically by plotting a smoothed cumulative frequency* distribution curve Of the 181 patients composing the nor mal group 27 had one or more values outside the normal range

All 7 radioiodine tests studied were relatively accurate for diagnosis of exophthalmic goiter since in only few instances did the values overlap those of the normal range for any test studied Among the 92 patients with exophthalmic goiter there were no values within the normal range for 6-hour up take or for thyroidal iodide clearance and only 4 8% of the values were within the normal range for conversion ratio

For the diagnosis of exophthalmic goiter in this series de termination of 6 hour uptake and determination of thyroidal iodide clearance were the most precise of the tests studied distinguishing sharply between the patients with exoph thalmic goiter and those in whom there was no thyroid dis ease The 24 hour conversion ratio also was quite precise in diagnosis of exophthalmic goiter with minimal overlap of values between the group with hyperthyroidism and the group without thyroid disease The 6-hour thyroidal collec tion test is the simplest and most rapidly performed and re quires the least radioactivity hence it is best for the require ments of a routine radioiodine test

The radioiodine test that is perhaps most widely used at

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After administration of Telepaque® thyroid uptake of radioactive iodine rapidly returns to previous levels The general belief that cholecystograms long influence radioactive iodine uptake might be exaggerated Normal uptake may be resumed as early as 3 days after a cholecystogram and a low uptake as long as 1 year later but the low uptakes may or may not be related to the cholecystography

Serum protein bound iodine was determined in 21 euthyroid patients after cholecystograms Of 9 measurements made 2 months or less after cholecystography all were over 8 µg /100 ml Of 12 determined 2 12 months after only 1 was over 8 µg /100 ml The largest measured discrepancy between protein bound and total iodine levels occurred at 10 weeks

The half life of radioactive Priodax® in the rat guinea pig and human is short briefer than a tracer dose of radioactive iodine There is little deiodination in the human and a fast excretion mainly in the urine is mostly as Priodax® and Priodax® glucuronide Most of the Priodax® in human serum apparently becomes associated with protein or bound but considerable amounts remain unbound and a small amount is presumably iodide

There is a faster turnover of iodide in the hyperthyroid than the euthyroid patient and therefore an early return to normal or elevated levels of thyroid radioactive iodine uptake following ingestion of iodine compounds One week after a cholecystogram hyperthyroid patients had uptakes in the high normal or high range after 4 weeks most euthyroid patients had uptakes in the low normal or normal range

► [This paper another by Newman and Cupp (J Clin Endocrinol 17:94 1957) which gives very similar data shows that the radioactive iodine metabolism returns to base line long before the chemical determination of protein bound or butanol extractable iodine Astwood has recently stated (Tr A Am Physicians 1957) that after certain types of gall bladder dyes the blood iodine may apparently be *permanently* elevated. The I^{131} uptake however is not affected after a few week —Ed]

Total Free Tocopherols in Serum of Patients with Thyroid Disease The extent of muscle disease at a given level of clinical hyperthyroidism varies from mild subjective weakness to severe disabling myopathy Increased oxygen consumption hypercreatinuria and depletion of muscle creatine seen in rodents made deficient in tocopherol suggested that ex

present as a diagnostic aid is the 24 hour uptake by the thyroid It is simple to perform and requires minimal co operation by the patient and a minimal dose of radioiodine The test for 6 hour uptake proved better than the test for 24 hour uptake being completely effective in separating euthyroid persons from those who had exophthalmic goiter including those in whom the 24 hour uptake fell within the normal range

It may be difficult to decide whether a patient with nodular goiter is or is not hyperthyroid Results of radioiodine tests are much less decisive here than in diagnosis of exophthalmic goiter Although such results are usually within the normal range in patients with nodular goiters who are euthyroid they also are frequently normal in patients who have toxic nodular goiters

Likewise radioiodine tests are of limited usefulness in diagnosis of myxedema Determination of 6 hour uptake or 24 hour uptake particularly the former is of considerable discriminatory value in diagnosis of myxedema Nevertheless clinical interpretation of abnormally low uptakes is hindered by the knowledge that exogenous iodine from various sources frequently is the cause of such findings in normal or hyperthyroid persons

► [The fact that the 6 hour uptake is better than the 24 hour test should simplify the mechanics of testing Although a single counting period may be fairly satisfactory we have frequently found 3 separate counts at 2 6 and 24 hours to be helpful in separating the patients with high initial uptakes and rapid turnover rates (e g following subtotal thyroidectomy) from those with rapid uptakes because of hyperthyroidism since in the former the curve is flatter or may even have begun to fall at 6 hours whereas in the latter it usually continues to rise for 24 hours —Ed]

Effects of Organic Iodine Compound (Priodax®) on Tests of Thyroid Function Certain iodine containing compounds associate with serum proteins and are measured as protein bound iodine This protein bound iodine which normally consists mainly of thyroxin is thus artefactually elevated Some of the organic iodine compound remains unassociated and raises the total iodine Uptake of radioactive iodine may be reduced Studies were conducted by D Ward Slingerland[1] (Tufts Univ) in experimental animals and humans using radioactive Priodax® and observing the effect of Telepaque® on thyroid uptake

(1) J Cl E doc I 17 8 93 J ua y 1957

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haustion of tocopherol stores in patients with hyperthyroidism caused the muscle symptoms Sholem Postel[2] (Harvard Med School) surveyed the concentration of tocopherols in serums of patients with thyroid disease

Analysis of thyrotoxic patients as to age sex duration of illness extent of weight loss clinical severity of thyrotoxicity and prominence of muscular weakness did not permit accurate prediction of tocopherol levels but generally patients with severe Graves disease had the lowest levels whereas those with mild or relatively asymptomatic cases had values approaching normal Patients with hypothyroidism tended to increased levels of tocopherol

A strong inverse relation was thus demonstrated between levels of thyroid function and concentration of total free tocopherols in serum In the reported series of 115 patients serum levels of more than 1 2 mg /100 ml ruled out untreated Graves disease and a concentration of less than 1 7 mg /100 ml was inconsistent with diagnosis of hypothyroidism There was a strong positive correlation between concentrations of total cholesterol and the tocopherols in serum *Fat soluble tocopherols share the reciprocal relation of* serum lipid concentrations and levels of thyroid activity Total tocopherol stores aberrations in their metabolism or the physiologic significance of the observed changes cannot be estimated on the basis of serum concentration of tocopherols alone There is no recognized lesion in man comparable to any of the tocopherol deficiency syndromes of animals However the hypermetabolism and possible increased tocopherol requirement of patients with toxic diffuse goiter results in a unique state The patient with thyrotoxicosis may provide the best situation in which to find a human tocopherol deficiency state expressed as an acute reversible muscular dystrophy

Chronic Thyrotoxic Myopathy Report of 2 Cases is presented by R Hoffenberg and L Eales[3] (Univ of Cape Town) Loss of weight is a cardinal symptom of thyrotoxicosis General muscular wasting is an integral part of the process and often striking Occasionally a local disorder of muscle with severe wasting and profound weakness attends thyroid disease

(2) J Clin Invest 35 1345 1356 Dec mb r 1956
(3) So th Afr can M J 30 1 46 1249 Dec. 29 1956.

Chronic thyrotoxic myopathy is characterized by severe muscular atrophy frequently involving only a few muscle groups and often overshadowing other manifestations of thyrotoxicosis It is rare judged by the few cases reported Most patients were men usually in middle life Onset was gradual with slow progression of symptoms over months or years Predominant features were loss of weight muscular weakness and atrophy Severe muscle cramps were frequent Muscles of the shoulder girdle and pelvis were maximally affected with lesser involvement of peripheral muscles The

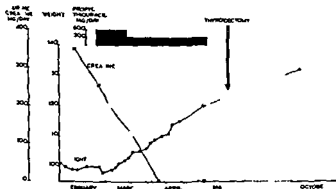


Fig 117 —Response to th rapy (Cou t y f H ff be g R nd Eal L South African M J 30 1246-1249 Dec. 29 1956)

thyroid was usually enlarged and most patients had a fine tremor Eye signs suggested hyperthyroidism in about one third Other manifestations were not prominent Most showed a raised BMR and a few exhibited high urinary excretion of creatine In the few patients who had radioactive iodine tests and serum protein bound iodine examinations these confirmed hyperthyroidism Therapy of the thyrotoxicosis corrects the myopathy

Man 49 had loss of strength tremor increased sweating irritability and nervousness dyspnea and palpitation Weight dropped from 142 to 128 lb Pain stiffness and weakness of thigh muscles were prominent A BMR was reported as 85% Methylthiouracil induced weight gain to 141 lb symptomatic improvement and slowing of the pulse but treatment was discontinued because the thyroid became markedly enlarged. Thereafter his weight continued to fall despite good appetite he lost strength and became shaky and dyspnea and palpitation recurred At this time he was ex

tremely wasted eyes were staring and the thyroid was firm and symmetrically enlarged He had gross wasting of the small muscles of the hand with fixation of several joints Thigh muscles were grossly wasted

Serum alkaline phosphatase 24 hour urine creatinine/creatine excretion and BMR were elevated and muscle biopsy revealed some variation in thickness of muscle fibers with focal areas of sarcolemma nuclear proliferation

Propylthiouracil induced a steady response with weight gain and reduced pulse rate but the thyroid again enlarged Subtotal thyroidectomy was performed Histologic diagnosis was diffuse toxic hyperplasia Muscular strength and general health progressively improved Weight rose steadily after operation (Fig 117)

► [The mechanism by which thyrotoxic myopathy occurs is not clear Postel s observations clarify this problem somewhat. It would be of theoretical interest to investigate the effects of tocopherols on muscle function in thyroid disease however practically speaking treatment of the hyperthyroidism is the treatment of choice for this type of myopathy — Ed.]

Long Term Follow up of Nontoxic Nodular Goiter Effect of Clinical Selection on Observed Incidence of Malignancy Management of nontoxic nodular goiter is controversial Some insist that all such goiters be extirpated because of risk of malignancy Others have shown thyroid cancer to be rare whereas nodular goiter is common True prevalence of malignancy in nontoxic nodular goiter is estimated to be less than 1%

Joseph E Sokal[4] (Yale Univ) reviewed records of inpatients at Grace New Haven Community Hospital diagnosed as having nodular goiter or thyroid cancer between 1921 and 1945 The population of New Haven is relatively stable a significant number of residents were born in goitrous regions of Europe and few patients were subjected to surgery therefore such a study should provide direct evidence of the incidence of malignancy among unselected nodular goiters Patients known to have cancer of the thyroid were not included

Among an estimated 8 000 patients with nodular goiters treated conservatively between 1921 and 1945 8 thyroid cancers were diagnosed Five of these less than 0 1% were probably malignant at the time of the original description Three developed years later *Of the 8 patients 4 died of thyroid* cancer 1 of other causes without cancer and 3 are alive without recurrence 7 22 years postoperatively Some additional

(4) A M.A A ch. I t M d 99 60 69 Ja uary 1957

thyroid cancers may have developed among these persons and been treated elsewhere but this is unlikely Follow up totals about 3 000 patient years No clinical evidence suggesting a new thyroid cancer has been noted during this time

Authors who have studied this point agree that incidence of malignancy among nontoxic nodular goiters is low Deaths from thyroid cancer among conservatively treated patients have been so few that they would almost certainly have been exceeded by operative deaths had all patients with nodular goiter been subjected to surgery Conservative management of selected cases of nontoxic nodular goiter appears thoroughly justified

Most nontoxic nodular goiters need not be extirpated Enlarging firm discrete tumors of the thyroid should be removed Surgery is indicated for relief of pressure Clinical estimate of the number of nodules in a goiter is of little value Uninodular goiters frequently turn out to be multinodular The pre ence of 2 benign nodules confers no protection against the development of a third malignant one Observation is justified in almost all cases to determine whether a nodule is enlarging and the effect of treatment with desiccated thyroid or iodine Prognosis in thyroid cancer depends mainly on the biologic characteristics of the tumor and is little affected by minor delay in surgical treatment

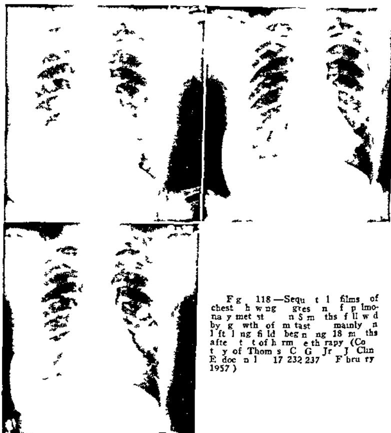
► [The paper continues to develop the line of evidence which indicates that indiscriminate removal of all nodular goiters is unnecessary and undesirable (see p evious discussions in 1954-55 YEAR BOOK p 602 1955 56 p 601 and 1956-57 pp 659 and especially 661) —Ed.]

Hormonal Treatment of Thyroid Cancer Two factors may be involved in induction of malignant neoplasms Certain stimuli (initiating factors) incapable of inciting tumor formation may alter cell physiology and biologic potential so that a stimulus (promoting factor) which follows may lead to neoplastic growth According to Colin G Thomas Jr[5] (Univ of North Carolina) carcinoma of the thyroid fits this scheme A carcinogen alone may induce few tumors but if followed by a goitrogen incidence of tumor is strikingly high—much greater than with the goitrogen alone

Most of these tumors depend on thyrotropic hormone and often the cour e of malignant thyroid disea e in human be

(5) J Clin. Endocrinol. 1 23- 37 February 19 7

ings can be influenced by administration of desiccated thyroid Of 9 patients with carcinoma of the thyroid given 120 300 mg desiccated thyroid daily for 3 weeks to 28 months 3 did not respond and the disease progressed rapidly Tumor growth was inhibited in 2 but the histology did



Fg 118—Sequ t l films of chest h w ng gres n f p lmona y met st n S m ths f ll w d by g wth of m tast mainly n l ft l ng fi ld beg n ng 18 m ths afte t t of h rm e th rapy (Co t y of Thom s C G Jr J Clin E doc n l 17 232 237 F bru ry 1957)

not change 2 showed regression by clinical examination radiologic study and biopsy (Fig 118) 1 exhibited simultaneous regression and progression of pulmonary metastases and 1 observed only 3 weeks showed no clinical or morphologic changes

The behavior of certain thyroid cancers might be explained by need of a promoting factor It would account for

the relatively higher incidence of papillary thyroid cancer in younger age groups subject to the physiologic stresses of puberty adolescence and pregnancy the multiple foci of origin and the increasing malignancy of the same tumor with age

All tumors in the 9 patients studied did not completely depend on thyrotropic hormone for continued growth Autonomy of growth seems to be quantitative In some neoplasms some cells may still depend on thyrotropic hormone for growth while others do not If thyrotropic hormone can promote development of thyroid cancer prolonged use of excess thyrotropic hormone seems hazardous Prolonged therapy with any antithyroid drugs particularly in children when continued several years should be questioned unless exogenous thyroid is administered

Suppression of thyrotropic hormone by desiccated thyroid would appear most valuable in patients who have had the thyroid carcinoma excised Suppression of thyrotropic hormone would inhibit remaining normal thyroid tissue from undergoing malignant change or subsequent growth of residual neoplasm

► [This observation confirms previous reports (Balme 1955 56 YEAR BOOK p 602) and substantiates the rationale of treatment suggested by Sturgeon *et al* (1954 55 YEAR BOOK p 606) This consists of preventing hypothyroidism by administering exogenous thyroid and stimulating I^{131} fixation by the metastases intermittently with thyroid stimulating hormone immediately before administration of therapeutic doses of I^{131} — Ed]

Thyroid Cancer in Childhood and Adolescence Between 1936 and 1956 James D Majarakis Danely P Slaughter and Warren H Cole[6] (Univ of Illinois) treated 9 boys and 6 girls aged 5 20 Average duration of the mass in the thyroid or neck was 4 3 years

Of the 15 lesions 7 were papillary adenocarcinoma 5 adenocarcinoma and 3 adenocarcinoma in adenoma (adenoma malignum) Preoperative diagnosis was made in 7 patients who all had cervical node metastases Diagnosis was made at surgery in 3 of whom 2 had metastases in the neck Diagnosis was made postoperatively in 5 none had radical neck operations but 4 received intensive irradiation In the 9 patients with obvious metastases to the neck nodes radical neck dissection was performed besides thyroidectomy

(6) J Ch E doc i ! 16 1487 1490 Nov mb 1956.

All patients were living but 2 of the 9 with radical neck dissection had had recurrence 1 and 4 years respectively after operation The longest survival time has been 18 years Of the entire series 53% were living 1 10 and 47% 10 or more years after operation Of the 10 patients aged 15 or under all had had x ray therapy to the head and neck in infancy or childhood the dosage varying from 200 to 625 r None of the patients aged 16-20 had had irradiation

► [Prolonged survival of children with thyroid carcinoma is also de scribed by a group from the Mayo Clinic (Hayles *et al* J Clin Endocrinol 16 1580 1956) Although thyroid nodules in children deserve im mediate attention one must be somewhat conservative in treatment lest the cure prove worse than the disease —Ed]

CARBOHYDRATE METABOLISM

► [As information has increased about the role of the various foodstuffs as sources of energy in the tissues it has become apparent that the great importance initially attributed to carbohydrate was exaggerated. The fol lowing study emphasizes the small part carbohydrate plays in the energy metabolism of muscle Studies such as this lead one to suspect that in most tissues carbohydrate may prove to be of importance chiefly because it supplies important intermediates (for instance those needed for main tenance of the Krebs citric acid cycle for the formation of pentose pre cursors of nucleic acid and for the regeneration of the important reducing substances triphosphopyridine nucleotide and diphosphopyridine nucleo tide) All these functions can be served by metabolic pathways in which oxidation plays only a small part —Ed

Quantitatively Minor Role of Carbohydrate in Oxidative Metabolism by Skeletal Muscle in Intact Man in Basal State Measurements of Oxygen and Glucose Uptake and Carbon Dioxide and Lactate Production in Forearm are reported by Reubin Andres Gordon Cader and Kenneth L Zierler[7] (Johns Hopkins Univ) Skeletal muscle accounts for some 40% of body weight Since it is the largest mass of tissue its metabolism may be a major factor in total body economy

Oxygen consumption by resting muscles of the forearm is vigorous If it is representative of oxygen uptake by all skel etal muscles then muscle accounts for 35-40% of total body oxygen uptake at rest and following a 16-hour fast In con trast muscle glucose uptake is relatively small only 20% of total body glucose uptake

Venous lactate concentration always exceeded arterial

(7) J Cl I v t 35 671 68 Ju 1956

concentration Muscle produced lactate continuously even at rest and in the presence of active oxygen consumption On the average 60% of glucose uptake by forearm muscles was accounted for by lactate production with wide individual variations The remaining glucose was assumed to be oxidized completely Its oxidation could account for only about 7% of oxygen uptake Glucose abstracted from blood is only a minor fuel for skeletal muscle under these conditions

The mean respiratory quotient of forearm muscle was 0 80 suggesting that the major noncarbohydrate material which serves as the substrate for oxidation in forearm muscle is lipid

Parity and Incidence of Diabetes Mellitus More women than men have diabetes mellitus In youth there is little difference in sex incidence but after age 45 women outnumber men at least 3 2 (Harris Joslin *et al*) In a survey of 953 patients (583 women and 370 men) D A Pyke[8] (Radcliffe Infirm Oxford England) found an approximately equal sex incidence under age 45 but a predominance of women over 45

Part of the sex difference is due to there being more middle aged and elderly women than men in the general population When this factor is eliminated and the remaining figures compared with those for the parity of normal women aged 45-49 the excess of women with diabetes is confined to those who have borne children The relative excess of women increases with each degree of parity A woman with five children has about three times as much chance of developing diabetes as one with none

Based on a sample of the 1951 census the theoretical number of women with no children who had diabetes would have been 100 the actual number observed was 91 with one child the expected was 67 and observed 69 with two children the expected was 63 and the observed was 89 With parity of 3 4 5 6 7 and more the expected number was 34 18 9 6 and 9 respectively while the observed number was 58 44 27 25 and 60 respectively Thus in women para II VII there was a 1 4 6 7 fold increase in the expected incidence of diabetes a statistically significant figure with P $(\chi^2) < 0\,001$ n=1

Parity does not lead to diabetes earlier in life Age at di

(8) La t 1 818 8 1 J 2 1956

agnosis is similar for all degrees of parity *The effect of parity* on incidence of diabetes does not merely reflect greater incidence of obesity since about 31% of nulliparas were overweight The preponderance of women with diabetes is found among those of normal weight and underweight If the menopause were of etiologic importance an excess of women with diabetes would be expected in all parity groups but this is not the case

Diabetes and Altered Carbohydrate Metabolism in Patients with Cancer Previous studies indicated a significant increase in incidence of diabetes in cancer populations and

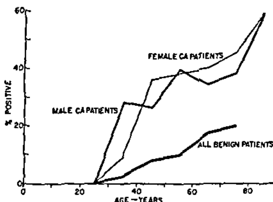


Fig 119 —Incidence of diabetic glucose tolerance curves by age and sex (Courtesy of Glicksman A S and Rawson R W Cancer 9 1127 1134 Nov Dec 1956)

of cancer in patients with diabetes mellitus Arvin S Glicksman and Rulon W Rawson[9] (Memorial Hosp New York City) studied a cancer population for frequency of diabetes mellitus and compared findings with those of patients who had benign conditions Consecutive cases were studied excluding only those with fever or those who recently received steroids or nitrogen mustards

All were tested by a standard oral glucose tolerance test 1 75 Gm glucose/kg body weight and were considered positive only if the blood sugar (1) was more than 200 mg/100 ml at any time during the test (2) was greater than 100 mg/100 ml at 2 hours and (3) did not return to the fasting level in 3 hours Tests were performed 48 72

(9) Cancer 9 1127 1134 Nov D 1956

hours after admission during which interval the patient received a diet of 1 800 2,200 calories containing 200 250 Gm carbohydrate

A total of 950 patients were studied Diabetic glucose tolerance curves were observed in 36 7% of the cancer group and only 9 3% of the benign group The same general differentiation between the cancer and the benign lesions was noted in each organ system involved

Mean age of patients with cancer was 58 years for those with benign lesions 50½ years When male and female patients were analyzed separately there was no difference between the 2 groups in age incidence of diabetic glucose tolerance curves (Fig 119) Weight distribution of diabetics and nondiabetics was essentially identical and no abnormalities could be attributed to obesity or cachexia No particular religion was disproportionately represented in either group

Not only is diabetes mellitus clinically manifest more frequently in the cancer population but a subclinical or latent aberration in carbohydrate metabolism is more frequent also Pathogenesis is unknown The consistently greater frequency of hyperglycemic responses in patients with endocrine tumors or tumors of organs that respond to endocrine stimulation suggests that hormone environment may be involved Convergent lines of investigation relate impaired carbohydrate tolerance growth hormone and cancer

► [Somewhat similar observations have been reported by Marks and Bishop (J Clin. Invest. 36 254 1957) The high incidence of diabetes in cancer patients need not necessarily lead to the authors conclusions about the importance of growth hormone. The fact that cancer patients are sometimes undernourished and that an appreciable portion of their carbohydrate intake may be shunted into the formation of pentoses to be used for nucleic acid synthesis by the cancer suggests that other influences must also be taken into consideration —Ed.]

Hypoglycemia in Primary Carcinoma of Liver Though only 7 cases have been reported the association is not as rare as this paucity would indicate and observations on 27 Chinese patients with primary carcinoma of the liver 9 of whom had hypoglycemia are presented by A J S McFadzean and Yeung Tse Tse[1] (Hong Kong) Diagnosis was confirmed by needle biopsy and 24 patients came to autopsy

As the intravenous dextrose tolerance test did not give a plateau curve in any of the 9 patients with persistent hypo

(1) A M A. A h I t. Med. 98 720 731 December 1956.

glycemia it is concluded that this type hypoglycemia is fundamentally distinct from that reported in other liver diseases Rate of disappearance of injected dextrose did not differ significantly from that in healthy controls even when the liver function was grossly deranged In 4 patients with cholangiocarcinoma a plateau curve developed

The fall in serum inorganic phosphorus level during the intravenous dextrose tolerance test varied from patient to patient and in the same patient Commonly the fall was significantly less than that in normal subjects After onset of hypoglycemia the response was constant in each patient and in all was less than 10% Apparently the dextrose is diverted from peripheral utilization and the diversion is due wholly or in part to the tumor The diversion depletes the glycogen reserves in the residual liver The demand for dextrose by the tumor persists in the fasting state and reserves are rapidly exhausted The demand is then met by gluconeogenesis Once demand exceeds supply hypoglycemia results

Significant quantities of glycogen were demonstrated in the hepatoma in the presence of hypoglycemia suggesting that glycogen within the tumor is not available in the body economy That cortisone raised the fasting blood sugar level to normal in 2 of 3 patients suggests that it may have a place in management of such cases

Natural Course and Prognosis of Juvenile Diabetes Priscilla White (Tufts Medical School) reviewed records of 1 072 children with diabetes mellitus who have lived 20 years or more representing 28 7% of all juvenile cases treated at the Joslin Clinic to 1955 These patients are no longer children 61% are aged 30 39 years 18% are aged 20 29 20% are aged 40 49 and 1% are over age 50 The oldest is 56 Duration of diabetes to January 1956 or to death varied from 20 to 42 years with 30% surviving 30 years or more Age at onset and sex distribution was typical of juvenile diabetes peak age 11 years sex distribution even Hereditary data were compiled in 57% and supported the thesis that transmission is through mendelian recessive genes

Onset of symptoms typically was sudden and the disease was first recognized in many by diabetic coma Despite this virulent onset remissions occurred in one third occasionally

(2) Diabetes 5 44 450 N Dec 1956

even to a normal glucose tolerance curve Insulin requirement increased gradually to ½ unit/pound body weight Diabetes seemed more affected by linear growth than by gain in weight Linear growth was satisfactory in most patients Weight after age 20 was maintained normal or subnormal in nearly 90%

Sexual maturity seemed delayed in girls since menarche appeared at a median age of 15 years compared with the normal median of 13 years Sterility was no problem but

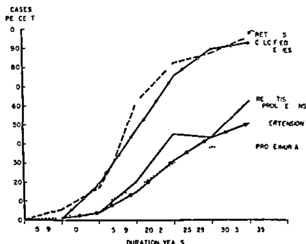


Fig 120—I d f sc l l on in f m l w th d bet (Court y f Wh t P Diabetes 5 445-450 N Dec 1956)

fetal wastage was high with an abortion rate 2½ times normal and perinatal loss 6 times normal

With varying intensity and frequency the 1 072 patients developed the major complications of diabetes coma infections neuritis and vascular damage They had abscesses and carbuncles pyelonephritis tuberculosis and osteomyelitis Neuropathy occurred in 26% of women and 20% of men most commonly as acroneuritis with gastrointestinal neuropathies in second place Vascular damage was by far the most common complication At 35 years duration of diabetes nearly all patients showed lesions 94% had calcified arteries 93% retinopathy 59% neovascularization 53% hypertension and

44% nephropathy These lesions were not observed in the first 5 years rarely in the first 10 and with increasing frequency after 15 years of diabetes mellitus Lesions were rare under age 20 but were prevalent by age 30 (Fig 120)

Significant progressive and lethal lesions involved arterioles capillaries and venules with venule dilatation due to loss of venule tone and arteriolar constriction Intravascular aggregation of erythrocytes perivascular edema and hyaline deposition followed These changes were also observed in children of diabetic mothers 16% in those with normal glycemia 51% in those with hyperglycemia

Cardiorenal vascular lesions caused death in 87 5% Nephropathy alone accounted for half the deaths Coma sepsis and tuberculosis formerly the chief causes of death now account for only 0 6 0 6 and 1 2% of the total respectively Median age at death was 32 median duration of diabetes was 22 years

Diabetes and vascular damage may be interrelated by gene linkage physical signs a complication or any combination of these Children of diabetic mothers have shown the vascular pattern characteristic of diabetes These may be prediabetics or heterozygotes who carry only the vascular changes as part of the inherited recessive defect However poor chemical control of diabetes was statistically and significantly correlated with frequency and severity of the vascular lesions

► [The relentless progress of the vascular concomitants of diabetes is still the most important problem in this disease The fact that vascular degeneration may occur before the carbohydrate defect is detectable suggests that control of the carbohydrate manifestations of the disease is only of minor importance in preventing development of the complications The results reported by White are splendid as compared with the prognosis in the preinsulin era nevertheless they are clearly unsatisfactory I wish I knew how to improve them!—Ed]

Personality and Intelligence of Diabetics Conflicting evidence has been published on the intelligence and personality of patients with diabetes mellitus Most evidence is clinical involving few cases and only suggestive of the actual personality To investigate this problem further, A J Kubany T S Danowski and C Moses[3] (Univ of Pittsburgh) administered the Minnesota Multiphasic Personality Inventory and Stanford Binet tests to a sample group of children with diabetes

(3) Diabetes 5 46 -467 Nov Dec 1956

If there is a particular personality pattern it should appear in a profile analysis However compared with control subjects of approximately the same age there is no significant difference These patients were compared with normal populations and none of the control subjects had to maintain the daily regimen to which the patient with diabetes must adhere No control had to visit a clinic or private physician periodically nor were they asked to take time out of daily routine to provide much personal information Because the patients still compared favorably in terms of normal personality the results are even more striking Perhaps the abnormalities reported by many other investigators which have been generally applied to all patients with diabetes occur after onset of the disease as a reaction to the patients perception of their condition to the physician and the imposed clinical regimen

With the Minnesota Multiphasic Personality Inventory as the measuring instrument the juvenile diabetic is no more predisposed to behavior abnormalities than are normal subjects The patient with diabetes mellitus has an IQ in the middle of the normal range There is no relation between age at onset of diabetes and abnormal behavior for any of the personality variables

► [Exasperated physicians wrestling with recalcitrant and uncooperative diabetic patients have often felt that these patients must be psychiatrically deranged Apparently this is not so—at least in Dr Kubany s practice —Ed]

Clinical Correlates of Kimmelstiel Wilson Lesion Franklin H Epstein and Vito Joseph Zupa[4] (Yale Univ) reviewed 137 autopsy protocols of patients who had had diabetes and died between 1944 and 1953 Of these 37 (27%) had nodular glomerular lesions of the Kimmelstiel Wilson type Clinical records of these patients were compared with those of 37 other patients who had diabetes and in whom autopsy was done

About three fourths of patients with Kimmelstiel Wilson lesions had pyelonephritis Each had arteriosclerosis of the larger renal vessels Elevated nonprotein nitrogen was noted at some time in 60% and 12 died with a nonprotein nitrogen level of over 100 mg /100 ml In the comparison series 60% had arteriosclerosis but arteriosclerosis of large vessels

(4) New England J Med. 254 896 900 May 10 1956.

was prominent in only 7 Pathologic evidence of pyelonephritis was present in only 8 and an elevated nonprotein nitrogen in only 3

Of the patients with Kimmelstiel Wilson lesions 28 were women and average age at death was 55 not notably different from diabetic patients without glomerulosclerosis Average age at onset of diabetes was 41 years in patients with lesions and 51 in those without while duration of diabetes was 14 and 9 years respectively

Hypertension was consistently recorded in 80% of patients with Kimmelstiel Wilson lesions Albuminuria was present in 86% Average length of life after albuminuria was detected was 3½ years with a range of 1 17 years and its presence carried a grim prognosis Only 1 patient had neither albuminuria nor hypertension but marked nodular glomerulosclerosis was found at autopsy

Average insulin requirement was 0 10 units in 17 patients with Kimmelstiel Wilson lesions and in 22 patients without 10 30 units was required in 11 and 6, respectively and 30-60 units in 9 patients each Acidosis developed in the same number of patients in each group Thus about as many patients with intercapillary glomerulosclerosis required the same amounts of insulin as did those without the lesions and the frequency of diabetic acidosis in patients with nodular glomerulosclerosis did not differ from that in diabetic patients without this lesion

The study does not support the view that a specific or unique type of diabetes characterized by infrequent episodes of acidosis and a decreasing requirement of insulin, is associated with the Kimmelstiel Wilson lesion

► [The high incidence of pyelonephritis noted by Epstein and Zupa has also been described by others In many instances it is the infection rather than the vascular lesion which kills the patient Some of the blame for the frequence of pyelonephritis must undoubtedly be laid to the common practice of catheterizing diabetic patients especially those in coma and especially women on admission to the hospital The catheter is a dangerous instrument which should be used with the respect it deserves In the long run it seems likely that more people die each year as a remote result of catheterization than from such major operative procedures as thoracotomies or craniotomies —Ed.]

Renal Puncture Biopsy in Diabetic Patients Ch Darnaud Y Denard G Moreau and J M Suc[5] report histologic studies on 20 patients who were classified into four groups ac

(5) S m e hop Pa is 3 407-417 D c 20 1956



F g 121 (top) —Gl m rul w th d ff l on M k d d ph li t ning m x m m p ph ral port on
F g 122 (t) —Gl m l w th gn fi t d ff d d fi t ly nod l l on
F g 123 (b tt m) —Gl m l w th l g h l od l m K mm l t l W lson bod oc t 3 w h gn fi t d ff se l
(Court y f D rn d Ch t al S m hop P 3 407 417 Dec 20 1956)

cording to stage of progression of renal lesions In 6 patients significant changes were found in glomeruli tubules and vessels and nodular lesions were numerous i e the Kimmel stiel Wilson syndrome was anatomically evident In 7 characteristic lesions were of lesser intensity but could be diagnosed as Kimmelstiel Wilson glomerulosclerosis Five patients displayed only discrete nonspecific renal lesions In 2 no kidney lesions were detectable On the whole degree of involvement of glomeruli tubules and vessels was comparable Conversely phosphatase studies could not be correlated with any anatomic or clinical factor

Renal lesions revealed by puncture biopsy involve essentially the vascular system of the kidney i e the malpighian corpuscles or arterioles These essential lesions are apparently accompanied secondarily by involvement of the epithelial lining of tubules and of interstitial tissue In the glomeruli a continuous series of events unites the circumferential and advanced nodular lesions to earlier diffuse lesions Histochemically these diffuse thickenings appear to be of definite physiopathologic significance and are an integral part of the anatomic syndrome of the diabetic kidney The deposits stain deeply with PAS showing an intense violet purple color and are definitely acidophilic demonstrating the glycoprotein nature of the substance which causes diffuse thickening of glomerular structures This permits differentiation of diffuse involvement in the diabetic glomerulus from that of glomerulonephritis in which hypercellularity and fibrosis are consistently present Diabetic renal lesions seem to progress from diffuse thickening (Fig 121) to nodules of hyalinosis (Fig 122) circumscribed masses (Fig 123) and sclerosis

Anatomicoclinical findings in these 20 patients and in 2 series previously reported by others (total of 52 cases) demonstrate that specific renal lesions are present in almost half (22 of 52) Most often these are clinically latent Only when they are very advanced and usually combined with significant nonspecific lesions do clinical and biologic symptoms appear In themselves these signs are relatively unimportant but they become significant when seen in combination e g edema hypertension albuminuria and diabetic retinopathy most often in elderly women with diabetes of long duration

Serum Lipids and Polysaccharides in Diabetes Mellitus David Adlersberg Chun I Wang Harold Rifkin James Berkman George Ross and Clement Weinstein[6] (New York) estimated lipid fractions cholesterol phospholipids total lip ids neutral fats glucosamine and total polysaccharides bound to protein in 73 normal control subjects 38 patients with uncomplicated diabetes mellitus 12 with diabetes and early retinopathy and 16 with fully developed Kimmelstiel Wilson syndrome

In patients with uncomplicated diabetes serum concen tration of these substances remained within normal limits The earliest increases of serum glucosamine and polysac charides were found in patients with diabetes who had early retinopathy Serum cholesterol and phospholipids remained within normal limits Patients with fully developed diabetic glomerulosclerosis showed elevation of all lipid fractions serum glucosamine and polysaccharides

It is suggested that the blood changes may precede de generative alteration of the tissue and depo ition of protein carbohydrate and protein lipid compounds in the retina and renal glomerulus. Perhaps the increases of serum lipid and carbohydrate may be pathogenetically related in develop ment of diabetic retinopathy and glomerulosclerosis Whether lipids and carbohydrate fractions show parallel in creases or whether one precedes the other remains to be investigated

► [The inve tigation of the carbohydrate-containing proteins and their importance in the development of diabetic complicat ons is in its infancy The correlat ons described above may later lead to information about the pathogenesis of the lesions —Ed.]

Fatal Acute Myocardial Infarction in Diabetic Patients Wilbur A Thomas Kyu Taik Lee and Erwin R Rabin[7] (Washington Univ) studied the clinical and autop y data on 94 diabetics who died of acute myocardial infarction and compared them with corresponding features in 406 patients (seen during the same 44 year period) who died of acute myocardial infarction but did not have diabetes

There were no patients with juvenile diabetes in the se ries an unexpected finding which disagrees with the impres sion that early development of diabetes is often followed by

(6) D b te 5 116 120 M Ap 1956
(7) A M A A h. I t Med. 98 489-494 Oct be 1956.

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Renal lesions revealed by puncture biopsy involve essentially the vascular system of the kidney i e the malpighian corpuscles or arterioles These essential lesions are apparently accompanied secondarily by involvement of the epithelial lining of tubules and of interstitial tissue In the glomeruli a continuous series of events unites the circumferential and advanced nodular lesions to earlier diffuse lesions Histochemically these diffuse thickenings appear to be of definite physiopathologic significance and are an integral part of the anatomic syndrome of the diabetic kidney The deposits stain deeply with PAS showing an intense violet purple color and are definitely acidophilic demonstrating the glycoprotein nature of the substance which causes diffuse thickening of glomerular structures This permits differentiation of diffuse involvement in the diabetic glomerulus from that of glomerulonephritis in which hypercellularity and fibrosis are consistently present Diabetic renal lesions seem to progress from diffuse thickening (Fig 121) to nodules of hyalinosis (Fig 122) circumscribed masses (Fig 123) and sclerosis

Anatomicoclinical findings in these 20 patients and in 2 series previously reported by others (total of 52 cases) demonstrate that specific renal lesions are present in almost half (22 of 52) Most often these are clinically latent Only when they are very advanced and usually combined with significant nonspecific lesions do clinical and biologic symptoms appear In themselves these signs are relatively unimportant but they become significant when seen in combination e g edema hypertension albuminuria and diabetic retinopathy most often in elderly women with diabetes of long duration

venously produce angina During hypoglycemia the patients experienced flushing of the face generalized warmth sweating weakness and sleepiness occasional mild headache dizziness jitteriness and hunger Hexamethonium given intravenously before insulin had no consistent effect on the symptom or response of blood glucose serum electrolytes and ECG In 1 patient semicoma developed and intravenous glucose therapy was necessary another remained in insulin shock for 2 hours yet in neither did angina pectoris or the ECG changes develop that had consistently appeared during exercise The ECG changes during hypoglycemia were similar to those in normal subjects given insulin These abnormalities were associated with decreases in blood glucose and serum potassium The T wave changes were similar to those observed in other hypopotassemic states These observations suggest that dangers from insulin induced hypoglycemia in patients with coronary artery disease may on occasion have been overemphasized

► [Hypoglycemic attacks have caused concern among physicians responsible for the treatment of diabetes chiefly because of danger of permanent damage to the organs of arteriosclerotic patients The chief organs for which concern has been felt are the brain and the heart No serious doubt exists of the permanent ill effects of hypoglycemia in some patients with cerebral arteriosclerosis We have seen patients develop hemiplegia during or immediately following acute hypoglycemic episodes and have followed several who had temporary neurologic defects during hypoglycemia which cleared after the blood sugar was restored to normal Since the brain is fairly dependent on carbohydrate as a substrate these findings are not surprising The heart is much less dependent on carbohydrate for its energy and the cardiac ill-effects of hypoglycemia have therefore usually been attributed to the reaction to low blood sugar—especially the release of epinephrine The preceding paper does not support this concept. A cursory reading might mislead one to believe that hypoglycemia is unimportant in patients with coronary insufficiency since the electrocardiographic changes of myocardial ischemia were not seen Arrhythmias developed in 3 patients however and a diminished serum potassium (which might be expected to exaggerate the effects of digitalis if this were present) was observed in all Although I am a little surprised at the bland nature of the electrocardographic changes in these subject I think the evidence here reported confirms the danger of hypoglycemia in patients with coronary insufficiency

The anticipated alterations of hemodynamics *were* observed in the following study —Ed.]

Effects of Insulin Hypoglycemia on Renal Hemodynamics Renal disease and insulin hypoglycemia occur frequently in the clinical course of diabetes mellitus H V Murdaugh Jr[9] (Duke Univ) measured the effective renal plasma flow

(9) J Lab & Cl Med. 48 69 75 J ly 1956

arteriosclerosis with early death However 10 patients had *diabetes before age 40 their ages at death were significantly* less than those of nondiabetics with acute myocardial infarction

Before 1940 acute myocardial infarction in this series was significantly commoner among men than women yet in the *same period among diabetics there was no significant differ* ence between the sexes in incidence of infarction After 1940 myocardial infarction was significantly more common among diabetic women than among diabetic men incidence was still significantly greater among nondiabetic men than *among nondiabetic women*

The over all incidence of acute myocardial infarction among the diabetic patients was considerably higher than its incidence in the nondiabetic autopsy population There was no significant difference between age at death of the two *groups however Comparative figures for other anatomic or* clinical features of nondiabetic and diabetic patients who died of acute myocardial infarction generally showed in significant differences

Effects of Insulin Induced Hypoglycemia in Patients with Angina Pectoris Before and after Intravenous Hexametho nium were studied by Walter E Judson and William Hol lander[8] (Boston Univ) Transitory ECG changes in nor mal subjects after administration of insulin have been at tributed to the direct action of hypoglycemia and/or the effect of epinephrine released in the circulation Clinical ob servations suggest that hypoglycemia from even small doses of insulin in patients with diabetes mellitus and coronary artery disease may precipitate angina or even coronary thrombosis

Eleven patients with hypertensive cardiovascular and/or coronary artery disease with angina pectoris were studied After exercise typical angina associated with ECG evidence of myocardial ischemia developed in each After intravenous administration of insulin serum potassium decreased in all and 7 showed ECG changes parallel to changes in blood glucose and serum potassium *but they were unlike the myo* cardial ischemic changes observed during exercise Arrhyth mia developed in 3 patients In none did insulin intra

(8) Am. H art J 5 198 209 A gu t 1956

as a lifesaving measure and thereafter remained severely disabled and restricted to a chair bed existence

Conservative management of foot lesions particularly of infections is often rewarded by successful preservation of intact feet and legs Such an approach requires weeks or months of hospitalization with attendant expense but is worth while if the patient is able to leave the hospital on his two feet Major amputations may require only 2 3 weeks of hospitalization but the patient is left demoralized and de pendent a burden to family community and self

The most important aspect is prevention of infections in the feet which should be washed daily especially between the toes Epidermophytosis should be treated Redness ulcer ation or discoloration must be reported to the physician im mediately Such changes are considered serious and usually necessitate hospitalization Heat strong chemicals and pres sure from new shoes must be avoided

Patients with infection should be followed carefully by the surgeon and internist Wide local incision should be per formed early and repeated as often as necessary to insure re moval of slough and provide adequate drainage from all pockets of pus Osteomyelitic metatarsals should be removed Dorsalis pedis pulses may return after edema subsides It is important to differentiate true gangrene from necrotic slough since necrotic slough has a better prognosis Re moval of a toe or a transmetatarsal amputation may be ade quate in some cases of true gangrene but many require higher amputation Below the knee amputation is recom mended in patients with good popliteal pulses who are can didates for prosthesis

CASE 1—Woman 60 showed an infection after the foot was stepped on 2 weeks earlier She had had symptoms of diabetes for 1 month A large area of fluctuation near the heads of the 1st and 2d metatarsals was found on the dorsum of the foot All toes were cyanotic and no pulses were felt in the foot Diabetes was con trolled Midthigh amputation was advised by the surgical service but refused Penicillin local drainage and wet soaks were started the 2d toe and distal phalanx of the 1st were amputated and the wound on the dorsum was closed by skin graft She walked out of the hospital 3 months after admission

CASE 5—Woman 69 was hospitalized for marked dyspnea She had had diabetes for 6 years and had been taking 10 units of insulin daily Two weeks before admission a water blister on the left toe

and glomerular filtration rate before during and after insulin hypoglycemia in normal subjects and patients with diabetes mellitus with and without renal disease Hypoglycemia severe enough to produce symptoms is associated with reduced effective renal plasma flow and glomerular filtration rate and increased filtration fraction

Subjects who had hypoglycemia without weakness and sweating did not show the renal hemodynamic changes found in those who had symptomatic hypoglycemic reactions In patients with diabetes mellitus the blood glucose level at onset of the study was high and the decrease after insulin pronounced but not productive of symptoms No decrease in effective renal plasma flow or glomerular filtration rate occurred Patients with diabetes mellitus and renal disease who had hypoglycemic symptoms showed decreases in kidney function similar in degree to those of normal subjects with symptomatic hypoglycemia

Changes in renal hemodynamics were related neither to absolute blood glucose concentration during hypoglycemia nor to degree or rapidity of fall in blood glucose The only positive correlation was the appearance of hypoglycemic symptoms The decrease in effective renal plasma flow with a lesser decrease in glomerular filtration rate is typical of the pattern of changes resulting from renal efferent arteriolar vasoconstriction seen in shock fright and following epinephrine administration The clinical syndrome of hypoglycemic reactions resembles that following epinephrine administration The pattern of response in renal hemodynamics to hypoglycemia the presence of sweating and frequent increase in pulse pressure in subjects with symptomatic hypoglycemia are compatible with an increase in epinephrine activity It is proposed that changes in renal hemodynamics result from epinephrine activity secondary to hypoglycemia

Management of Foot Lesions in the Elderly Diabetic is reviewed by David Hurwitz[1] (Harvard Med School) Long standing diabetes is commonly associated with coronary artery disease retinopathy nephropathy and peripheral vascular disease Among elderly patients with diabetes peripheral vascular disease is one of the leading causes of hospitalization Formerly these patients had early high amputation

(1) J Am G riatr Soc 4 648 653 J ly 1956

as a lifesaving measure and thereafter remained severely disabled and restricted to a chair bed existence

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Case 5 —Woman 69 was hospitalized for marked dyspnea She had had diabetes for 6 years and had been taking 10 units of insulin daily Two weeks before admission a water blister on the left toe

was treated with potassium permanganate soaks and powder On examination she was in congestive failure had tachycardia and fe ver and the left great toe was swollen dark and necrotic The 2d and 3d toes were fissured and black with seropurulent discharge bone was visible and pedal pulses were not palpable

Diabetes and congestive failure were controlled the 2d toe and metatarsal head and distal phalanx of the 1st toe were excised the plantar aspect was drained and saline soaks were applied A month after discharge she was readmitted with osteomyelitis of the re maining portion of the 1st toe which cleared after 10 days of penicillin therapy She was discharged after 3½ months of hos pitalization Cardiac status limits activity but she has a functional foot

► [Conservative treatment is more difficult than the traditional radical approach The physician and surgeon must work in close co operation In our experience adequate debridement of the infected area has taxed the skill of the surgeon much more than amputation Although conservative management is more difficult and expensive than amputation it is safe and the ultimate successful result cannot be measured in terms of expense An excellent paper emphasizing the same approach was published by Oak ley Catterall and Martin (Brit M J 2 953 Oct 27 1956) They point out that many of the lesions seen in diabetic feet are a result of neurop athy rather than inadequate circulation In neuropathic patients the prognosis is better than in those with lesions due to arteriosclerosis —Ed]

Rare Type of Femoral Sciatic Neuropathy in Diabetes Mellitus Two cases are reported by Bengt Skanse and Karl Gydell[2] (Univ of Lund) Diabetic neuropathy may manifest itself in different ways In elderly patients with mild dia betes the characteristic findings of diabetic neuropathy are paresthesias nocturnal pain impaired sensitivity and loss of deep reflexes Paresis and muscular atrophy are usually absent More unusual neuropathies include severe hip and thigh pain weakness and wasting of leg muscles without sensory loss This rare involvement mainly motor was pres ent in both patients The disorder may be mistaken for other neurologic conditions or vascular disorders of the limbs

Woman 58 had severe grinding pain in the right leg for 4 months It was worse at night and was relieved by walking For 6 weeks the leg had been weak No numbness or paresthesia was present and she had no history of diabetes mellitus Examination revealed hypertension normal arterial pulsations grade II hyper tensive retinopathy weakness of the right iliopsoas and quadriceps and absent right patellar reflex Laboratory studies showed hyper glycemia glycosuria and cerebrospinal fluid protein of 72 mg /100 ml Diabetes was well controlled by diet Pain in the right leg persisted for 3 weeks the right quadriceps became atrophic and then slight improvement occurred About 3 months later a similar se quence occurred in the left leg She died of bronchopneumonia

(2) Acta med sc nd nav 155 463-468 1956

Autopsy revealed degeneration of the peripheral nerve myelin sheaths and hypertrophy of the endoneurium of degenerated neurofibrils Anatomic diagnoses were multiple peripheral neuropathy and early arteriolosclerosis of the cerebrum and spinal cord hyper tensive heart disease and purulent bronchitis

This is a rare neuropathy involving mainly the femoral and sciatic nerves in a patient with asymptomatic diabetes of unknown duration Neural damage was confined to motor symptoms and pain without sensory loss Although neuro logic findings regressed in one leg while they progressed in the other autopsy revealed equally severe bilateral changes Diabetic myelopathy did not cause this type neuropathy The clinical course suggested degeneration of peripheral nerves plus ome other factor probably metabolic

Atonic Neurogenic Bladder as Manifestation of Diabetic Neuropathy is reported in 2 cases by John Balfour and G J Ankenman[3] (Vancouver B C) Vesical dysfunction is be lieved to occur in 1 2% of patients with diabetes mellitus In older men the lesion may be combined with prostatic or bladder neck obstruction and accurate differentiation is often impossible No definite correlation exists between age and sex or duration and severity of the diabetes

Symptoms are typical of a chronically distended sensory paralytic bladder similar to that of tabes dorsalis and often called pseudotabes diabetica The neuropathy of pernicious anemia and alcoholism may produce the same clinical pic ture The lesion is usually advanced when recognized The patient may notice lengthening intervals between micturi tions or have nocturnal incontinence Considerable straining may be necessary to initiate the urinary stream Other geni tourinary disorders may be present such as impotence or sphincter disturbances

Residual urine is variable and usually high Cystometry shows a long low pressure curve with lack of sensation Un inhibited contractions are absent Cystoscopy reveals a nor mal bladder neck and no trabeculations in the wall The sen sory nervous system is chiefly involved and motor disturb ances are rare Neurologic examination reveals pain pares thesia and areflexia Any of these findings with an atonic neurogenic bladder in a patient with diabetes mellitus is sufficient for diagnosis

Treatment includes regulation of diabetes and treatment of

(3) J Urol 76 746-752 December 1956

any urinary infection Bladder neck resection in trained hands is considered so safe it should probably be regarded as conservative early management

► [In addition to these neurologic complications a syndrome of gastric retention resulting from neurologic changes in diabetics has been described by Kassander (National Meeting of the American College of Physicians quoted in *Modern Medicine* p 224 May 15 1957) —Ed]

Specific Resistance to Bovine Insulin is reported in a patient with diabetes by H H Kreutzer, J J Moors and R Verhille[4] (Heerlen The Netherlands)

Woman 59 during examination for rheumatoid arthritis was found to have diabetes which for 2 years was controlled by a 1 500 calorie diet without insulin Insulin treatment with Organon a bovine insulin was then begun and though the original dose soon had to be increased diabetes progressed Eventually 2 000 units daily failed to control the blood sugar level Clinical investigation showed no evidence of liver damage A dose of 1 700 units of Novo insulin (40% bovine and 60% hog insulin) promptly resulted in serious hypoglycemia The blood sugar level was controlled with 240 units of this mixed insulin She was then given pure hog insulin and the requirement was reduced to 140 170 units (54-61% of dosage of mixed insulin) As a clinical test bovine insulin administered in similar doses had no effect on the blood sugar level showing that she was still resistant to this insulin Eventually allergic manifestations of urticaria developed when bovine insulin was given Semi lente insulin from hog pancreas was then obtained, and she was finally stabilized and maintained in good condition on a dosage of 60 units

Insulin preparations from various manufacturers were tested with the same results i e she was resistant to beef insulin and responded satisfactorily to hog insulin A mixture of 0 5 ml serum and 0 15 units of insulin was injected intraperitoneally into guinea pigs and the blood sugar level determined 2 hours afterward With normal serum and bovine insulin the level was —22 mg and with mixed bovine and hog insulin —19 mg/100 ml With her serum and bovine insulin the level was +7 5 mg and with mixed insulin —6 mg When her serum was mixed with pure beef insulin the level was —17 mg and with pure hog insulin —41 mg These experiments demonstrated that her serum neutralized bovine insulin to a considerable degree but did not neutralize hog insulin Her serum gave a positive hemagglutination in a dilution of 1 320 with bovine insulin but hemagglutination was negative in a dilution of 1 10 with hog insulin Control serum was negative to both bovine and hog insulin

The clinical findings can be explained only on the basis of an antigen antibody reaction A possible reason for difference in antigenic function of beef and pork insulin may be that bovine hog and sheep insulins differ chemically Amino

(4) Nederl. tijdschr gen k 100 3598 3610 Dec 8 1956

acids 8 9 and 10 according to Sanger s (1954) formulae in bovine insulin are alanine serine and valine in hog insulin treonine serine and isoleucine and in sheep insulin alanine glycine and valine

From these observations the following hypotheses emerge (1) As resistance to insulin sometimes is due to antibodies a specific reaction may be suspected justifying treatment of resistant patients with insulin from a different source (2) This may be valid also for diabetics who need less than 200 units/day and hence are not clas ed as insulin resistant but in whom insulin need has increased (3) Increased in sulin requirement during an intercurrent infection may also be explained by assuming that nonspecific antigens result ing from reaction to infection may exaggerate an otherwise weak insulin antigen (anamnestic reaction) Possibly in such instances insulin requirement would also be decreased by use of a product from some other animal

Investigation of Prolonged Insulin Resistance in Case of Diabetes Mellitus is reported by J R Presland and C M Todd[5] (Univ of Otago) Resistance to insulin has been at tributed to production of excessive quantities of insulin antagonizing hormones abnormally rapid insulin destruc tion or formation of antibodies neutralizing insulin

Woman 57 obese had diabetes discovered 15 years before initially controlled with 40 units of insulin daily but requiring no insulin for the next 12 years A furuncle then developed on the hand and she was given 35 units daily A month later insulin re sistance developed and increased until 500 units daily was insuffi cient to control diabetes Diabetic coma developed requiring 3 000 units of insulin Thereafter insulin requirements increased reach ing a maximum of 5 000 units daily and then gradually declined At discharge 19 weeks after the episode of coma she was taking 600 units daily During the time of the increasing insulin require ments he had recurrent infections She died 9 months later of coronary artery insufficiency

Samples of the serum of the patient taken when the in sulin dosage was 2 000 units a day and injected into rats caused profound hypoglycemia which was fatal in about an hour unless the blood sugar level was restored by injections of glucose The serum of the patient also stimulated glycogen formation in the isolated rat muscle When insulin was with held from the patient the serum had no such effect on gly cemia of the rats These experiments indicated the blood of

(5) Q rt J Med 25 275 284 Ap 1, 1956

the patient contained a large amount of insulin, capable of exerting its characteristic effect on the blood sugar level of the rat Control experiments with normal human serums and those of diabetic patients receiving up to 50 units of insulin daily had no significant effects on blood sugar levels of rats These experiments do not support the hypothesis that the serum of the patient was able to bind or otherwise inactivate insulin

The remarkable feature of this case was the presence of large amounts of insulin associated with the beta lipoprotein of the plasma This indicates that insulin resistance was not due to inadequate absorption or excessive inactivation of insulin but to defective response in the tissues

Case of Insulin Resistance Treated with Corticotropin is reported by J Kleeberg D Diengott and J Gottfried[6] (Jerusalem)

Man 62 with severe diabetes took up to 600 units of insulin daily but the diabetes could not be regulated Although intravenous administration of insulin was more effective than the subcutaneous route it was abandoned because it apparently provoked angina Because of the possibility that the insulin resistance might be caused by an insulin antibody corticotropin was given—3 days intravenously and then as a gel in doses of 100 mg daily The insulin necessary to control the diabetes decreased progressively to about 50 units daily and the patient was considerably improved subjectively Corticotropin was discontinued after 25 days Three days later arterial occlusion and gangrene developed in the left leg During this period he became resistant again requiring up to 400 units of insulin daily Rather than give a fresh course of corticotropin lente and semi lente insulin were administered Insulin requirements were reduced gradually and he was discharged on a regimen of 130 units daily of subcutaneous semi lente insulin

Evidence of an antibody mechanism was achieved by passive transference of skin sensitivity to insulin (Prausnitz Kustner method) to a normal person Bioassay technics showed that prior incubation of the serum of the patient with insulin decreased the anticipated hypoglycemic response when this quantity of insulin was injected into rats This anti insulin effect tended to parallel clinical insulin resistance

The marked therapeutic effect of corticotropin in this case supports the assumption that insulin resistance was due to an antigen antibody reaction

(6) J Cl Endocrin 1. 16 680 686 M y 1956

► [Although the 3 preceding papers present somewhat conflicting interpretations of the mechanism of insulin resistance there now seems to be good evidence that in many instances failure to respond to insulin is a result of specific (?) antibodies (1956 57 YEAR BOOK p 666) Koenig Weiger and Sowinski (J Lab & Clin Med. 47 867 1956) have also reported the presence of increased amounts of gamma globulin in a patient with hemochromatosis and insulin resistance After ACTH treatment the serum gamma globulin concentration was reduced and the patient became more responsive to insulin

The introduction of oral antidiabetic substances into the therapeutic armamentarium has produced an immense amount of practical and theoretical research. Over 150 papers dealing with this subject have been reviewed by the editor this year Symposia have been published on this subject in the *Canadian Medical Association Journal Metabolism* (November 1956) *Diabetes* (Jan Feb 1957) and the *Annals of the New York Academy of Sciences* (meeting of February 14 15 1957) to mention only a few All these symposia are worthy of serious study In the space afforded by this YEAR BOOK only a brief summary is possible Studies of the *mode of action* have shown that these substance are effective only when insulin is present although only a very small amount is needed The insulin can be of exogenous origin in a totally depancreatized animal It therefore appears unlikely that the drugs act chiefly by increasing insulin secretion or by blocking glucagon secretion They act in the absence of adrenal or hypophysis therefore their effect is not a result of inhibiting anti insulin secretions of these gland Mirsky s suggestion that they act by reducing the action of the insulin destroying enzyme system insulinase (1956-57 YEAR BOOK p 671) has been attacked by some observers both because the concentrations needed to achieve insulinase blockade in vitro are much larger than the plasma level seen in vivo and because these substances do not alter demonstrably the rate of disappearance from the blood of radioactive insulin preparations Neither of these arguments appears entirely satisfactory however since the liver might concentrate the antidiabetic substances to a higher level than the plasma and the amount spared by the antidiabetic preparations might be too small to be detected by changes in the rate of disappearance of tagged insulin from the blood (rather a gross method of measurement) but might still be enough to be of physiologic importance

It has also been suggested that the antidiabetic substances might work by reducing the rate of release of glucose from the liver as a result of slowing the rate of conversion of glycogen or glucose precursors (such as fructose amino acids pyruvic acid etc) to glucose Evidence has been produced to suggest that activation of phosphorylase (the enzyme responsible for breaking down glycogen to glucose 1 phosphate) may be blocked by the sulfonylurea agents If this is the only effect of the compounds however it is difficult to see why the presence of insulin is essential to their activity In summary therefore no completely satisfactory explanation of the physiologic activity of these substances has yet been proposed

Clinically little can be added to the initial report of Bertram (1956 57 YEAR BOOK p 667) The materials are not often effective in juvenile diabetics they are effective in more than half the adult diabetics tested. They are not effective in the presence of acidosis The following report one of many similar ones emphasizes some of these points—Ed]

Role of Sulfonylurea Derivatives in Management of Diabetes Mellitus Preliminary Report is presented by Ewen Downie Joseph Bornstein Bryan Hudson and Kathleen

Taylor[7] (Melbourne) The mode of action of sulfonylurea compounds on disturbed metabolic processes of diabetes mellitus is unknown These compounds cannot be regarded as insulin substitutes The failure of some patients in whom the plasma contains appreciable amounts of insulin to show a response to sulfonylurea compounds suggests that they do not act by facilitating insulin action

Further knowledge of the mode of action and some simple means of determining the response of the patient are necessary before general use can be recommended Some patients who have responded to BZ 55 (carbutamide) therapy become hyperglycemic and have glycosuria 10 days after treatment is stopped corresponding to the time required for excretion of the drug Others respond differently and no glycosuria or hyperglycemia is found for weeks after cessation of therapy This raises the suspicion of some severe interference with metabolic processes and possibly hepatic damage as yet unrecognized

Of 14 patients treated 1 had mental depression for 3 months and leukopenia which returned to normal while therapy was continued 1 had a photosensitive rash 16 days and 1 a rash on the face and otitis externa 27 days after therapy was started and 2 others had rashes 4 and 10 days after beginning treatment

At present there is potential danger in indiscriminate use of these compounds except under strict observation and biochemical control Sudden cessation of insulin therapy and replacement by any form of oral therapy particularly in young or thin insulin sensitive patients is likely to lead to severe ketosis and critical consequences

There is no simple or satisfactory test which can predict *which patients are likely to respond to BZ 55 therapy*

► [In view of the similarity of the chemical structure of carbutamide to that of the sulfonamides it was anticipated that toxic reactions might be a problem The following report outlines experience with the acute toxic effects of this compound —Ed]

Occurrence of Sensitivity and Side Reactions Following Carbutamide was investigated by W R Kirtley[8] (Univ of Indiana) Toxicity has been a primary concern since clinical trials of *carbutamide were started* because sulfonamides as a class cause side reactions Questionnaires were included in report sheets furnished to all investigators for reports of

(7) M J Australi 1 1072 1078 June 30 1956
(8) Diabetes 6 72 73 Jan Feb. 1957

toxicity of any sort Carbutamide has been supplied to 2 900 physicians and through them to over 7 000 patients Data have been obtained from almost half this group

Total incidence of toxic effects (table 1) is a cause of concern particularly if the drug is given over a long period Most side reactions are those of the sulfonamide drugs At the time of the report 8 fatalities (table 2) had occurred under conditions which indicated the drug might have contributed to death Undoubtedly sensitivity reactions do occur It is anticipated that final analysis will reveal an incidence which will not exceed 5%

TABLE 1—REACTIONS REPORTED FOLLOWING USE OF CARBUTAMIDE

	No cases		No cases
Rash	109	Acute edema	4
Anorexia, nausea vomiting	81	Crystalluria	3
Malaise lethargy fever	79	Thrombocytopenia	2
Agranulocytosis leukopenia	[illegible]8	Purpura	[illegible]
General allergy	[illegible]	Eosinophilia	2
Cardiovascul al	16	Headache	2
Exfoliative dermatitis	6	Psychosis	1
Acute anemia	6	Hypothyroidism	1
Jaundice liver function	6	Methemoglobinemia	1
		Tachycardia	1
		Sudden myocardial failure	1
		Unclassified	10

TABLE 2—FATALITIES FOLLOWING CARBUTAMIDE

Sudden myocardial failure	1
Sulfonamide sensitivity	[illegible]
Bone marrow depression	1
Dermatitis f l t	1
Acute pulmonary edema	1
Liver l em t	[illegible]
	8

A top y d t not y t labl

► [As a result of these reactions carbutamide was withdrawn from distribution on October 26 1956 Tolbutamide a compound which differs from carbutamide only in that the amine group has been replaced with a methyl group to produce a toluene rather than aminobenzene derivative has proved to be much less toxic It has been released for general use on prescription Studies of acute toxicity however do not answer the important question of the remote toxic effects of these substances Tolbutamide will be used not for days or weeks but for the duration of the patient's life Will we find in 10 years that late sensitivity reactions such

as have plagued the users of the sulfonamides will damage the blood vessels? No one can tell as yet

At present we feel that these substances should be used sparingly There is no evidence that tolbutamide is a substitute for insulin indeed its effects are quite different from those of the hormone The critical question is whether reducing the blood sugar without appreciably altering the rate of glucose utilization is important. Certainly the basic principles of good diabetic management still apply adequate dietary control insulin if needed prevention of obesity are all important In a few cases tolbutamide may prove to offer something of value to patients who are blind or otherwise find insulin hard to administer but for most diabetics the new drugs still appear experimental

The antidiabetic sulfonylureas are not the only substances which can produce hypoglycemia when given orally Further search for useful oral medications is continuing —Ed]

Hypoglycemic and Insulinase Inhibitory Action of Some Plant Growth Regulators Following demonstration of hypoglycemia and concurrent decrease in insulinase activity in rats treated with l tryptophan it was found that indole 3 acetic acid a potent plant growth hormone (auxin) and a derivative of l tryptophan not only inhibits the action of insulinase in vitro and in vivo but also induces marked hypoglycemia in rats when given by stomach tube I Arthur Mirsky Daniel Diengott and Gladys Perisutti[9] (Univ of Pittsburgh) who made the previous investigations report on indole 3 acetic acid and two related compounds indole 3 butyric and indole 3 propionic acids and a synthetic plant growth regulator p chlorphenoxyacetic acid

The three indole compounds produced significant depression of blood sugar levels when given orally to rats Even more pronounced hypoglycemic response followed oral administration of p chlorphenoxyacetic acid All were given in amounts of 4 mM /kg body weight By contrast administration of the related acids—acetic butyric and propionic —and indole itself produced hyperglycemia in the rats thus appearing to establish necessity of the presence of the intact auxin molecule All four plant hormones inhibited insulinase activity and again p chlorphenoxyacetic acid was more potent than the other auxins Thus the consequent hypoglycemic effects appear to be due to increase in availability of endogenous insulin

The data are typical of 16 synthetic auxins studied by the authors and reveal a hitherto unsuspected relation between plant and animal hormones

(9) Endocrinology 59 715 718 December 1956

CALCIUM PHOSPHORUS AND THE PARATHYROID GLAND

► Progress in our understanding of the physiology of bone and calcification has been rapid. Two reviews are worth the attention of physicians interested in this field. The Seminar on Bone Diseases which was presented in the *American Journal of Medicine* in January 1957 is concise and well organized. The paper by Neuman and Neuman in this symposium (p 123) is especially valuable in summarizing modern ideas about the physical chemistry of bone in a fashion which should be palatable to any physician. The Ciba *Symposium on Bone Structure and Metabolism* (Little Brown & Company 1956) is more detailed and advanced but should not offer great difficulties.—Ed.

Causes of Unsuccessful or Inadequate Parathyroidectomy in Hyperparathyroidism The only rational treatment of hyperparathyroidism is surgical removal of the hyperfunctioning tissue. This often is difficult since a detailed knowledge of topography and anatomy of the parathyroids is necessary. On the basis of experience with 92 patients operated on between 1930 and 1956 John Hellstrom[1] (Stockholm) details the reasons why results have been unsatisfactory in so many cases.

In 20 patients 22% either no hyperfunctioning parathyroids were discovered at the first operation or if such were detected an insufficient amount was removed. A total of 43 operations were performed in these 20 patients including 6 mediastinotomies but hyperparathyroidism persisted in 6. The commonest cause of incomplete parathyroidectomy was primary hyperplasia reportedly present in 10% of cases of hyperparathyroidism. The parathyroidectomy was frequently inadequate in such cases because the surgeon was unfamiliar with the condition, exploration was inadequate or too much excision was feared.

Multiple parathyroid adenomas, the cause of inadequate parathyroidectomy in 1 case, must not be confused with secondary compensatory hyperplasia which affects all the glands. Multiple adenomas have been estimated to be present in 6% of cases. In such cases hyperparathyroidism persists after removal of one adenoma.

In 3 cases the parathyroid adenoma was located in abnor

(1) Acta chir scandinav 112 79 91 1957

mal locations and was not found at the first operation In 1 it was embedded in the thyroid in another it was enclosed in a strip of thymus and in the third it was posterior to the larynx and esophagus

In 5 cases a thyroid adenoma was removed at the first operation in the mistaken belief that it was parathyroid adenoma In 3 cases inadequate exploration of the neck was the reason the adenoma was missed

Hyperparathyroidism is such a rare disease that only a few surgeons acquire any major experience with its diagnosis and treatment If all cases were sent to a central clinic many problems would be obviated It is of prime importance to make the diagnosis before surgery Only rarely should exploratory operations be undertaken on the more or less vague suspicion of hyperparathyroidism

Parathyroid Damage in Man Mechanism of Effect on Serum Levels of Calcium and Phosphorus In experimental parathyroidectomy serum calcium decreases before the serum phosphorus increases which supports the concept that parathyroid hormone acts directly to maintain the level of calcium in the serum Stephen M Krane (Harvard Med School) reviewed the records of patients who had permanent or transient symptoms of hypocalcemia following thyroidectomy for hyperthyroidism nodular goiter or carcinoma Ten patients were found in a 10 year period who had symptoms within 4 days of surgery and in whom a blood sample had been drawn at the first sign of tetany before any treatment had been given and analyzed for both calcium and phosphorus None of the patients had had symptoms suggesting hypocalcemia before thyroidectomy

In 7 of the 10 parathyroid damage incidental to thyroidectomy had decreased the serum calcium but with no or little increase in inorganic phosphate These observations indicate that damage to or removal of parathyroid tissue results first in hypocalcemia and is contrary to the hypothesis that the parathyroids act to maintain the level of calcium in the serum only indirectly by regulation of the inorganic phosphate in the serum through control of renal excretion of phosphate If the latter were true the serum phosphorus

(2) J Clin Endocrinol 17 386 389 M h 1957

should already be elevated by the time the calcium level is depressed

These observations and animal experiments support the concept that the parathyroids act directly to maintain the level of calcium in the serum

Cause of Hypercalciuria in Sarcoid and Treatment with Cortisone and Sodium Phytate According to Philip H Henneman Eleanor F Dempsey Evelyn L Carroll and Fuller Albright[3] (Boston) the hypercalciuria in sarcoid is not due to bone destruction but to a disturbed metabolic pattern closely resembling vitamin D overdosage

Calcium balance studies in 3 patients with sarcoid were contrasted with values in 13 normal controls All studies were performed on low and comparable calcium intake Fecal calcium in each patient with sarcoid was markedly below normal Urinary calcium was greater than could be accounted for by intake Cortisone hydrocortisone or sodium phytate increased fecal and decreased urinary calcium The mode of action of cortisone is unknown but sodium phytate apparently decreases absorption

The abnormalities in calcium metabolism were remarkably similar to hypervitaminosis D The subnormal fecal calcium excretions in the 3 patients could be explained by increased calcium absorption Hypercalcemia and hypercalciuria then would depend on and be limited in degree by calcium intake In 2 patients urinary calcium excretion was greater than intake which could not be explained by increased calcium absorption alone However the parathyroid hormone-like action of vitamin D has this effect because it increases urinary phosphorus excretion decreases serum phosphorus raises serum calcium and finally raises urinary calcium to levels greater than intake This hypercalcemia and hypercalciuria depend on bone for calcium The third action of vitamin D increased absorption of nitrogen sodium potassium magnesium and iron also occurs in sarcoid.

These studies strongly suggest though they do not prove that the hypercalciuria of sarcoid is due to endogenous hypervitaminosis D The abnormalities of calcium metabolism are (1) increased calcium absorption from the intestine (2) hy

(3) J Clin. Invest. 35 1229-1242, November 1956.

mal locations and was not found at the first operation In 1 it was embedded in the thyroid, in another it was enclosed in a strip of thymus and in the third it was posterior to the larynx and esophagus

In 5 cases a thyroid adenoma was removed at the first operation in the mistaken belief that it was parathyroid adenoma In 3 cases inadequate exploration of the neck was the reason the adenoma was missed

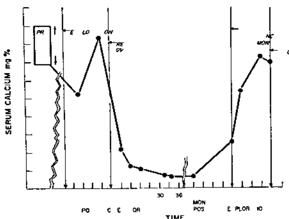
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(2) J Cl n E doc nol 17 386 389 Mar h 1957

Hypercalcemia in Malignant Disease without Evidence of Bone Destruction has been observed by Calvin H Plimpton and Alfred Gellhorn[5] (New York) in 10 patients since 1950 Symptoms were characteristic of hypercalcemic states including mental confusion In 3 removal of the tumor was followed by prompt fall in serum calcium In 1 recurrence of the tumor was associated with recurrent hypercalcemia In 7 patients no abnormality was found at autopsy in parathyroids bones or kidneys to account for the hypercalcemia



F g 124—Hyp l mia p t ent w th m (Court y f Pl mpton C H d G llh A Am J M d 21 750 759 N mbe 1956)

None had evidence of hyperparathyroidism vitamin D intoxication excess ingestion of milk and alkali multiple myeloma or Boeck s sarcoid

Hypercalcemia in metastatic malignancy is usually ascribed to bone metastases These 10 cases and several reported by others raise the question of whether tumors may produce a parathyroid hormone like substance

Woman 48 was hospitalized because of a 40 lb weight loss anorexia and vomiting Examination revealed cachexia a pelvic mass anemia and elevated sedimentation rate Serum calcium ranged between 15 7 and 17 9 mg /100 ml and serum phosphorus between 2 1 and 3 1 mg /100 ml A skeletal survey showed minimal demineralization with no changes of hyperparathyroidism or

(5) Am J Med 21 750-759 November 1956

percalcemia (3) increased calcium excretion in urine and (4) urinary calcium excretion greater than increased absorption alone can explain

The mode of action of ACTH cortisone and hydrocortisone in sarcoid is obscure These drugs may temporarily or permanently cause disappearance of sarcoid granulomas Sodium phytate appears to be the treatment of choice for hypercalciuria of sarcoid and its use is suggested for other instances of increased calcium absorption such as vitamin D poisoning idiopathic hypercalciuria and idiopathic hypercalcemia of infants

Hypercalcemia Due to Sarcoidosis Treatment with Cortisone Two cases are reported by R R McSwiney and Ivor H Mills[4] (St Thomas s Hosp Med School London) Hypercalcemia is an unusual complication but it is apparently the chief cause of renal impairment in sarcoidosis Renal dysfunction may be arrested or improved if the plasma calcium level can be lowered to normal and this can be done with cortisone By contrast cortisone and corticotropin in 2 other patients with normal calcium metabolism caused increased urinary excretion of calcium

Woman 57 had polyuria polydypsia and weight loss for 1 year She had peripheral epithelial opacities in each eye Urine contained a trace of protein and volume averaged 3 600 cc daily Specific gravity rose to 1 013 after 20 hours dehydration Intravenous pyelogram showed normal renal outlines no calcification poor concentration of dye but no delay in appearance The blood urea nitrogen level was 45 mg /100 ml Plasma calcium was 12 3 mg /100 ml phosphorus 4 4 mg protein 6 7 Gm with a 1 1 albumin globulin ratio and increased gamma globulin on electrophoresis

Tubular response to desoxycorticosterone acetate was defective and renal function was so impaired that results of parathyroid function tests could not be interpreted Liver biopsy showed non caseating tubercles consistent with sarcoidosis

Cortisone acetate was given orally 200 mg for 3 days and then 100 mg daily The plasma phosphorus level fell in 3 days and reached subnormal levels in 11 days and the calcium level became normal After 7 weeks of therapy renal function had improved slightly and blood urea nitrogen level had decreased to 24 mg /100 ml

► [The preceding two papers introduce a new method of treatment for hypercalcemia in sarcoidosis Observations with cortisone have also been reported by Phillips and Fitzpatrick (New England J Med 254 1216 June 28 1956) The use of sodium phytate appears to be the most specific available and is the treatment of choice —Ed.]

(4) Lancet 2 86 866 Oct 27 1956

The reason one endocrine organ should show evidence of deficiency before another is unknown All that can be aid is that more pituitary tissue is needed to support gonadal function than for thyroids and that adrenocortical maintenance requires least of all In man progressive pituitary disease is usually as ociated first with symptoms of gonadal depres sion and then thyroid and adrenocortical atrophy although there are well documented cases indicating selective failure of thyrotropin or ACTH

In animals with small pituitary remnants the adrenal is capable of at least a moderate degree of function despite ex tensive atrophy as indicated by an increase in weight of the remaining adrenal after unilateral adrenalectomy an ability to increase peripheral blood 17 hydroxycorticoid levels in respon e to immobilization stress and an output of 17 hydroxycorticoids from the adrenal vein at an appreciably higher level than that seen after total hypophysectomy

► The opportunity to study human beings after complete destruction of the hypopl ysis has b en si zed by two groups of investigators Some of the stud es of th Swedish group have already been reported in this section (Luft, Olivecrona and Sjogren 1955 56 YEAR BOOK p 647) The following two studies are of great importance becau e they emphasize the dif ferences between the handling of salt deprivation in hypophysectomized patients and in adrenalectomized ones and thus give further support to the evidence already outl ned in the Adrenal Gland section for the inde pendence of aldosterone secretion from pituitary function —*Ed*

Adrenal Function after Hypophysectomy in Man Remov al of the pituitary gland in experimental animals has been followed by adrenal atrophy Mortimer B Lipsett Charles D West John P Maclean and Olof H Pearson[7] (New York) report studies in patients from whom steroids were with drawn after surgical hypophysectomy or adrenalectomy for palliation of metastatic cancer

Generally the pattern of illness following withdrawal in hypophysectomized patients was similar to the effect een in adrenalectomized patients Anorexia malaise and weakness developed after a variable number of days and sometimes progressed to nausea and vomiting and severe asthenia Fe ver usually occurred and at times reached 104 F Hypoten sion was variable Glomerular filtration rate fell in each case studied Fa ting blood sugar rem ained unchanged in most of the patients serum potassium levels were unaltered and

(7) J Cl E docr 1 17 356 363 Ma ch 1957

metastatic malignancy Exploration of the neck revealed normal parathyroid glands and no adenoma At laparotomy a large pap illary adenocarcinoma of the ovary was removed Postoperatively serum calcium was 11 2 mg/100 ml then 10 3 mg and serum phosphorus 3 1 mg/100 ml Serum alkaline phosphatase showed a transient rise to 7 1 Bodansky units Serum calcium remained normal for 5 months A mass was then palpated in the lower right quadrant and the serum calcium rose to 13 4 and 15 5 mg with phosphorus 3 4 mg Skeletal x ray examination failed to reveal bony metastases She died suddenly at another hospital and autopsy was not performed Serum calcium levels are shown in Figure 124

► [A similar discussion is presented by Myers (Cancer 9 1135 1956) Hypercalcemia may be a serious or even fatal complication of malignant disease The cause of hypercalcemia remains obscure —Ed]

THE PITUITARY GLAND

► ↓The effect of gradual progressive destruction of the pituitary in human *beings is usually manifested first by hypogonadism later by hypothyroid* ism and by hypoadrenalism last of all (Peters German and Man Metabolism 3 118 1954) Under controlled experimental conditions the same sequence appears to occur in the dog as described below —Ed

Effect of Graded Hypophysectomy on Thyroid Gonadal and Adrenocortical Function in the Dog With removal of three fourths of the anterior lobe of the pituitary there is often no detectable endocrine deficiency To develop the usual atrophic endocrine changes that follow hypophysec tomy removal must be essentially complete William F Ganong and David M Hume[6] (Harvard Med School) studied the effect on target glands of removal of graded amounts of pituitary tissue in 30 dogs

There were not enough dogs with selective endocrine in sufficiency to permit definite conclusions but it was prob ably significant that none developed an isolated adrenocorti cal or thyroidal depression The sequence of lost endocrine function was gonad thyroid adrenals Removal of about 75% of the anterior pituitary resulted in no detectable en docrine abnormality but removal of 97 99% was associated with atrophy of all three target glands Removal of 75 95% was associated with gonadal or gonadal thyroidal insuffi ciency The gonadal atrophy seen in animals with gonadal deficiency alone was not as marked as that observed in ani mals which also had thyroidal and adrenal involvement

(6) Endocrin logy 59 293 301 Septembe 1956

verse effects or clinical symptoms when salt was restricted Sodium balance was obtained with equal facility during both high and low potassium intakes Thus alterations in potas sium intake or in the sodium potassium ratio alone did not affect aldosterone secretion

Previous investigations have erroneously attributed the control of sodium balance to the pituitary gland because determinations were done only in blood levels and the factor of water intoxication was not considered In addition ste roids were unavailable then and water retention increases if cortisone is deficient

Chromophobe Adenoma of Pituitary Gland Follow up Study on 60 Surgical Patients with Special Reference to Endocrine Disturbances is reported by Erik F Mogensen[9] (Univ of Aarhus Denmark) Chromophobe adenoma usually occurs in adults with its highest incidence in ages 45 50 The youngest patient in this series was a girl aged 13

The indications for surgery were limitation of the fields of vision in the presence of an enlarged sella turcica Endocrine disturbance was not considered an indication Approach was through a frontotemporal craniotomy and enucleation was intracapsular Six patients required reoperation for re currence Seven deaths occurred a primary operative mor tality of 12% Postoperative x ray therapy was given to 10 of the 53 survivors Indications for x ray varied but it was generally given because the tumor tissue removed contained a striking number of mitoses or nonchromophobe cells

Of the 60 patients the tumor was cystic in 6 and solid in 54 In 51 the histology revealed tissue consisting exclusively of chromophobe cells In 9 there were mixed eosinophils In only 1 patient were the eosinophils up to 50% of the cell total but since he showed no clinical signs of acromegaly or gigantism he is included Follow up studies were completed in all survivors Of 3 patients who died 2 had recurrences

Operative mortality was highest in patients with the larg est visual field limitation About one half showed total visual field improvement of both eyes after surgery Only 1 had to attend a school for the blind and none became completely blind Preoperative optic atrophy indicates prolonged pres sure and is a bad prognostic sign for return of vision In 11 patients with optic atrophy field defect improved in 37%

(9) A 1 endoc 1 4 135 152 Febru y 1957

the lowest 24 hour 17 ketosteroid excretion during withdrawal averaged 3 3 mg in the hypophysectomized patients —not significantly different from the average of 2 6 mg found in adrenalectomized patients not receiving steroid replacement The one marked difference was in serum sodium Whereas the level often falls during an adrenal crisis despite no external loss the hypophysectomized patients rarely had hyponatremia during adrenal insufficiency

In only 4 hypophysectomized patients did hyponatremia develop Two were receiving Pitressin® and 1 had a normal water exchange Apparently the presence of even mild diabetes insipidus prevented the development of hyponatremia which occurs after withdrawal of steroids Aldosterone in physiologic amounts did not alter the pattern of adrenal insufficiency which resulted from lack of 17 hydroxycorticosteroids

When compared with similar studies of adrenalectomized patients the pattern of steroid withdrawal symptoms tended to be milder The presence of antidiuretic hormone apparently is necessary for development of the hyponatremia associated with deficiency of 17 hydroxycorticosteroids in the absence of external salt loss

Regulation of Salt Metabolism after Hypophysectomy in Man Experiments in animals demonstrate conclusively normal sodium metabolism after hypophysectomy explained by the continued secretion of aldosterone in response to sodium restriction and its relative independence of corticotropin Aldosterone excretion has been shown to be normal in the patient with panhypopituitarism and to increase after hypophysectomy in response to sodium restriction These observations suggest that adrenal control of sodium metabolism is independent of pituitary function John P MacLean Mortimer B Lipsett Min C Li Charles D West and Olof H Pearson[8] (New York) studied all patients who had surgical hypophysectomy for metastatic cancer Hypophysectomy was judged complete in each

Sodium chloride balance studies in patients on regular low and high sodium diets showed responses which were the same as those of normal controls regardless of the type of replacement therapy The patients could adjust to large sodium loads without excess retention and there were no ad

(8) J Cl E docrin L 17 346-355 March 1957

responsible for the disturbed growth pattern Glomerular filtration rate and renal plasma flow are reported to be in creased in acromegaly but studies are incomplete Herbert Gershberg Henry O Heinemann and Harry H Stumpf[1] (New York Univ) describe a patient whose laboratory studies included renal function tests Autopsy revealed renal hypertrophy

Man 36 had had diabetes mellitus for 4 months before hospitali zation for bilateral fractures of tibial plateaus after minor trauma



Fig 125—Gl m l d l t d t b l f m k d y f c m g l mal (*A*) d rm l kid ey f m l of m g wh d d t m b l dent (*B*) N t t k g f gl m rul n *A* mp d w th m k gl m l *B* D ff t b l d m t l In k i y f m m g l m le (*A*) cap il ry b m t m mb n d l ghtly p m d cap l i y l p ong t d H m t xyl os d d f m ×190 (C rt y of G bbe g H *t l* J Cl E d l 17 377 385 M h 1957)

He had begun to grow rapidly at age 12 and an enlarged sella turcica was noted at age 23 At examination he was 78 in tall and weighed 230 lb he had acromegalic facies and a large body hands and feet Urinalysis showed glycosuria and acetonuria The plasma urea level varied from 23 to 33 mg /100 ml and the inor ganic phosphorus from 2 1 to 3 5 mg /100 ml The alkaline phos phata e level wa 5 9 units

Glycosuria and acetonuria continued after insulin therapy of 180 units daily but the acetonuria subsided when the dosage was raised to 270 units daily Filtration rate urea clearance and renal

(1) *J Cl E doc l* 17 377 385 *M h* 1957

compared to 79% improvement in those without optic atrophy. Field defects remained unchanged or became worse in a higher percentage of the patients with optic atrophy. The prognosis for visual acuity was better in those with no optic atrophy.

Before operation the signs of hypopituitarism were few and mild. Decreased gonadal function was the commonest and earliest disturbance. *However, hypogonadism does not* necessarily represent primary hypopituitarism but may be due to tumor pressure on the hypothalamus. The Kepler water test was normal in all the women and positive in 2 men. Serum sodium and potassium were normal in all patients tested and 17 ketosteroids excretion was decreased in only 4.

Postoperatively the decrease in gonadal function in both men and women was pronounced, the Kepler test showed marked disturbances in those patients classified hypocrine and 17 ketosteroid excretion was definitely decreased. Aldosterone excretion was assumed to be normal since all the patients maintained normal serum levels of sodium and potassium.

A number of postoperative complications occurred including diabetes insipidus in 1, transitory polyuria in 7, periodic anemia in 4, acute adrenocortical insufficiency in 2, transitory psychosis in 4 and biliary calculi in 1.

Impotence may respond to chorionic gonadotropin. Caution is indicated because such therapy is reported to increase the frequency of tumor recurrence. Adrenocortical substitution therapy is indicated only for subjective discomfort, particularly fatigue. It is of no benefit if laboratory studies do not confirm adrenal insufficiency. Hypothyroidism is treated with thyroid, but in the presence of adrenocortical insufficiency adrenocortical substitution should precede thyroid therapy. Pitressin® is effective in treating diabetes insipidus.

► [In this connection it is interesting to recall the report by Skanse and Arén cited on page 652 of disappearance of bitemporal hemianopsia in a patient with chromophobe adenoma after treatment with thyroid hormone. —Ed.]

Renal Function Studies and Autopsy Report in Patient with Gigantism and Acromegaly. *Hypersecretion of anterior pituitary growth hormone is generally considered to be*

composition most rapid with high fat less rapid with high protein and no loss for short periods of observation when given chiefly in the form of carbohydrate

With intakes of 2 000 calories a day weight was maintained or increased in 4 of 5 obese patients These same patients lost significant amounts of weight when their caloric intake was raised to 2 600 daily provided this intake was mainly fat and protein No defect in absorption of these diets accounted for the weight loss Body protein and carbohydrate stores were not depleted and could not account for the weight loss The loss was partly (30 50%) derived from total body water and partly (50 70%) from body fat

Apparently the composition of the diet can alter the expenditure of calories in obese persons the expenditure being increased when fat and protein are given and decreased when carbohydrate is given This effect is greater with fat than with protein The rate of insensible water loss was greater when intake of protein and fat was increased As the rate of weight loss varied so markedly with the composition of the diets on a constant calorie intake obese patients must alter their metabolism in response to the contents of the diet The change in insensible loss of water supports the suggestion that metabolism has been altered

► [These experiments appear to contradict those presented by Werner (1955 56 YEAR BOOK p 678) In Werner s study somewhat larger caloric intakes were used The single patient who lo t weight on a high fat diet in Werner s group had diarrhea The present authors seem to have controlled this possib l ty by performing balance studies In our own experience high fat diets often cause weight loss but this is usually a result of the anorexia developed by patients on a high fat low carbohydrate diet The danger of recently popularized low protein diets was emphasized by Joliffe (J A M A 161 1633 Aug 25 1956) Such diets are suitable only for restricted application under controlled conditions and should not be used without medical supervision —Ed]

Experimental Test of Glucostatic Theory of Regulation of Food Intake A popular current hypothesis is the glucostatic regulation of food intake which postulates that glucoreceptors in the central nervous system are sensitive to the rate at which they are utilizing glucose that low rates excite nerve activity leading to hunger sensations and food intake and high rates produce the opposite effect and that peripheral arteriovenous glucose differences are an index of utilization rates by the glucoreceptors To test this hypothesis Lionel M Bernstein and Morton I Grossman[3] (Fitzsimons

(3) J Cl I t 35 6 7 633 J 1956

blood flow (Tm_G Tm_{SO_4} Tm_{PAH}) were 60 100% above normal when corrected for body surface Calculated from the PAH clear ance the renal blood flow was 641 ml/minute Insulin dosages as high as 460 units daily did not control the glycosuria

After a sudden sharp pain in the left thigh and groin accompa nied by general weakness the patient perspired profusely The blood pressure and pulse were unobtainable and he died within a few minutes

At autopsy the most striking changes were seen in the kidneys The cortex was 1 2 cm thick The glomeruli and tubules were de *cidedly enlarged (Fig 125) The tubular epithelium contained* moderate deposits of glycogen Splanchnomegaly was pronounced and the lungs liver and kidneys were the heaviest on record The cause of death was not found

The increased glomerular filtration rate and Tm for PAH glucose and SO_4 reflect the increased size of the glomeruli *and proximal convoluted tubules seen histologically* If cal culated per gram of kidney weight the increase in function was not proportional to the organ weight The normal level of plasma inorganic phosphate was interesting and unexpected in view of the increased growth hormone activity Phos phate loss due to prolonged uncontrolled diabetes may have been responsible

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LIPIDS AND NUTRITION

Calorie Intake in Relation to Body Weight Changes in the Obese Many different diets are successful in reducing weight, and the principle of most is reducing caloric intake below the theoretical needs of the body However this con cept may be too rigid Most diets in common use radically alter the proportions of protein fat and carbohydrate Re cent investigations reveal more rapid loss of weight when the largest proportion of calories was supplied by fat than when supplied by carbohydrate A Kekwick and G L S Pawan* (Middlesex Hosp London) studied this problem in obese patients

Weight was lost by the obese patients in proportion to the deficit in caloric intake when the proportions of fat carbo hydrate and protein were kept constant at each level of cal orie restriction When caloric intake was kept constant at 1 000 daily weight loss varied greatly on diets of different

(2) Lan et 2 155 161 July 28 1956.

Physical examination and laboratory tests were negative except for hepatomegaly and a marked increase in serum vitamin A level The vitamin was discontinued One week later all leg and ankle pain had subsided and the tibial tenderness had disappeared Two weeks later she had no subjective complaints

► [Three similar cases in children have been reported by Pickup (Arch Dis Childhood 31 229 1956) —Ed.]

► ↓The mechanism by which hyperlipemia occurs is for the most part obscure Since hyperlipemia is often associated with the premature de velopment of atherosclerosis a great deal of effort has gone into studies of the pathogenesis of this abnormality The unusual situation in nephro sis has attracted the attention of those interested in renal vascular and lipid diseases A fortunate combination of these interests has led to the following paper which represents the culmination of a long series of studies by the authors —Ed.

Causal Role of Plasma Albumin Deficiency in Experi mental Nephrotic Hyperlipemia and Hypercholesteremia. In rats with nephrosis induced by injection of rabbit anti rat kidney serum the hyperlipemia and hypercholesteremia which develop are endogenous and cannot be ascribed to increased intestinal absorption or decreased intestinal excre tion Hepatic synthesis of cholesterol is not increased The rise in cholesterol and lipids is an isolated accumulation confined to the plasma apparently caused by failure of trans fer from plasma to the liver

Ray H Rosenman Meyer Friedman Sanford O Byers and Malcolm K Smith[5] (Mount Zion Hosp San Francisco) obviated hypercholesteremia and hyperlipemia by prevent ing external loss of urine in rats by ureteral ligation or by ureteral vena caval anastomosis This suggests that the cho lesterol and lipid abnormality observed in experimental ne phrosis is secondary to external loss of one or more plasma substances

Prevention or correction of the plasma albumin deficiency in the nephrotic rat inhibited the hypercholesteremia and hyperlipemia which otherwise would have occurred

The isolated rise of these plasma lipids is intimately re lated to and initiated by primary renal derangement Hy percholesteremia and hyperlipemia due to nephrosis do not appear in the absence of viable renal tissue However the rise of plasma lipids will not occur without external loss of some plasma constituent evidently albumin

Increased plasma albumin induced by ACTH in patients

(5) J Cl I t 35 5 2 532 M y 1956

Army Hosp) studied the effect of induced *hyperglycemia* on food intake and appetite in normal adults

The test treatments produced three distinct levels of ar terial venous and arteriovenous differences of blood glucose values at the time of the test meal Despite this test meal calories consumed did not differ significantly between treat ments and the amount of protein fat and carbohydrate was *unaltered*

dl Amphetamine and dexedrine® are commonly used to treat obesity because they are believed to reduce food in take In this study a single dose of dl amphetamine did not significantly decrease food intake as compared with all other glucose and saline test treatments This was contrary to ef fects reported in animals and man Perhaps significant an orexia might be demonstrated by repeated administration

No significant differences of appetite occurred between subjects given saline or glucose intravenously or intragas trically *Arterial venous and arteriovenous differences in* blood glucose had no effect on appetite in this study This corroborated the findings of the effects of blood glucose on food intake

Glucose given intravenously or intragastrically regularly produced elevations in arterial venous and arteriovenous differences in blood glucose levels as expected However consumption of food and intensity of appetite during *hyper* glycemia were not significantly different from control days when saline was given These results do not support the glu costatic hypothesis of Mayer

Hypervitaminosis A Report of Case in Adult is presented by Ray A Elliott Jr and Robert L Dryer[4] (Indiana Univ)

Woman 21 had pain in both legs and ankles for 1 week in creasing fatigue and insomnia *for 2 months intermittent low back* ache and mild bilateral hip pain for 1 month occasional aching pain in the left elbow and intermittent severe aching pain in the left foot She had slight swelling of both ankles and a bluish dis *coloration on the outer aspect without trauma In the preceding 2* months she had two episodes of sore mouth with small blisters on the tongue Urinary frequency had been present for a week Appe tite remained good there was no weight loss and the menstrual cycle was unaltered Questioning revealed she had been taking vita mins containing 10 000 units vitamin A 3 times daily on prescrip tion by her dermatologist for acne Without consulting him she had increased her daily intake to an average of 180 000 units

(4) J A M A *161 1157 1159 J ly 21 1956*

favors hypercholesteremia and atherogenesis and in time may lead to coronary artery disease hypertension and diabetes

Although measures directed toward maintaining normal cholesterol levels in these persons might alter their subsequent disease patterns they probably would not alter the fundamental metabolic defect

► [The epidemiology of atherosclerosis and its relationship to hyperlipemia or hypercholesterolemia has usually been studied retrospectively by analyzing blood after evidence of coronary disease has developed. This study reports a prospective study of this problem—a much more satisfactory approach. Unfortunately the author has elected to study only plasma cholesterol Since this is only one of the several moieties of plasma lipid believed to be abnormal in atherosclerosis and since there is reason to doubt that it is either primary or a good reflection of the important primary changes the study would have been more satisfactory with more complete data.—Ed]

Effects of Feeding Different Fats on Serum Cholesterol Level A widely differing incidence of coronary heart disease has been associated with a parallel difference in mean serum cholesterol levels in the multiracial community of Cape Town In each racial group the serum cholesterol level was highest in those of highest economic status and paralleled intake of foods rich in animal fat B Bronte Stewart A Antonis L Eales and J F Brock[7] (Univ of Cape Town) fed several different fats and oils to volunteers under controlled conditions and studied the effect on serum cholesterol levels

Two Europeans with coronary heart disease received a constant diet containing a moderate amount (50 Gm daily) of animal fat Six non European volunteers received a diet free of cholesterol and having only the fat contained in maize and bread To these diets various fats and oils were added one at a time in amounts of 100 Gm

Changes in the serum cholesterol levels coincided with changes in intake of fat and were paralleled by differences in the cholesterol contained in the β lipoprotein fraction (Fig 126) Results were unaffected by alterations in protein calorie or vitamin intake The changes appeared related to the quality rather than the quantity of change in fat intake In quantitatively equivalent amounts animal fats in the form of butter beef dripping beef muscle and eggs caused a rise in serum cholesterol Marine animal oils had the opposite effect on serum cholesterol either when fed alone after a fat free

(7) Lancet 1 521 5 6 Ap 28 1956

with nephrosis is associated with a fall of plasma cholesterol regardless of the pattern of diuresis Shifts of plasma cholesterol and albumin occur together reaching normal simultaneously No significant hyperlipemia and hypercholesteremia are observed consequent to renal damage in glomerular nephritis or in the many states in which nephrosis can occur unless urinary protein loss is excessive The cause of nephrotic lipemia seems not to be the renal lesion per se but the external renal loss of plasma albumin sufficient to induce hypoalbuminemia

Observations on Some Possible Precursors of Essential Hypertension and Coronary Artery Disease V Hypercholesteremia in Healthy Young Adults Caroline Bedell Thomas[6] (Johns Hopkins Univ) completed 1 000 cholesterol determinations on healthy medical students and correlated the findings with family histories Nearly 9% of the subjects had hypercholesteremia with levels of 300-434 mg /100 ml but none had any of the diseases usually associated with high cholesterol values These high levels occurred in both sexes and at all ages between 21 and 33 but none were found in subjects under age 20

There was a slight rise in mean cholesterol with age but the same subjects tested 4 7 years later showed no change Therefore not all young adults show increased cholesterol levels with age and some even show a decrease

The hypercholesteremic students belonged to families in which coronary disease hypertension diabetes and obesity appeared with unusual frequency A parent of 32% usually the father was affected by coronary disease in contrast to 12% of those with normal cholesterol values a highly significant difference Parents suffered from little strokes hypertension obesity diabetes nephritis and coronary artery disease

The findings suggest that the emergence of the hypercholesteremic trait in young persons can be linked with a familial tendency to cardiovascular disease especially coronary disease and diabetes that hypercholesteremia becomes apparent when physical growth and sexual maturity are complete and that persons susceptible to such environmental stresses probably inherit a metabolic defect which

(6) Am J M Sc 232 389 396 Octobe 1956

of fatty acids constituting the dietary fat may permit a better hypothesis If the nature of the modern diet is a major factor in development of coronary heart disease the disease may eventually be controlled and prevented

► [The effect of vegetable fat vs animal fat on the plasma lipids has been discussed here previously (1955 56 YEAR BOOK p 674) This effect is *probably not* due to the unsaturated fatty acids of vegetable oil (Jones Reiss and Huffman Proc Soc Exper Biol & Med. 93 88 1956) since a synthetic mixture of the known fatty acids of corn oil failed to exert the protective effect of natural corn oil in cholesterol fed chicks and since corn germ was more potent as an anti holesteremic agent than was corn oil Keys Anderson and Grande (Lancet 1 66 Jan 12 1957) confirmed these data in man by showing that the anticholesteremic effect of unsatu rated fats was not proportional to their degree of unsaturation since corn *oil is significantly more potent in reducing serum lipids than sardine oil* which is much less saturated.

The significance of these observations in man has sometimes been ques tioned since experimental production of atherosclerosis by a high fat diet has so far been produced only in normal rabbits and chicks

The fact that dogs failed to develop atherosclerotic lesions on a high fat diet unless they were first made hypothyroid raised a question of whether rabbits and chicks give a reliable picture of what occurs in man The pro *duction of xanthomatosis and atherosclerosis by a high fat diet in the adult* rhesus (Mann and Andrus J Lab & Clin Med. 48 533 1956) and Cebus monkey (Portman Hegsted Store Bruno Murphy and Sinisterro J Exper Med. 104 817 1956) suggests very strongly that experimental dietary data are applicable to some extent at least to the primates and therefore presumably to man For this reason the continuing accumula tion of data correlating the development of vascular disease with the fat content of the diet is of great importance The problem is being studied *on a worldwide basis as witness the next report*—Ed]

Effects of Dietary Fat Habits on Serum Cholesterol and Blood Pressure of Population in Group of Bosnian Villages G Zarkovic M Levi M Radovanovic and T Plecas[8] (Univ of Sarajevo) surveyed a random selection of peasants both Serbs and Moslems On the average caloric intake for the preceding year had been satisfactory although the percent age obtained from fat was relatively low (13 0%) and slight ly higher for Serbs than for Moslems

Serum cholesterol was low in the 231 persons examined ranging from 100 to 168 mg /100 ml and did not increase significantly with age Women below age 45 had lower cho lesterol levels than men Serbs in all age groups had higher cholesterol values than Moslems The lower proportion of fat in the diet and lower amounts of total cholesterol in Moslems as compared to Serbs strongly indicates a positive correlation between amount of fats in the diet and level of cholesterol In each group average concentration of choles

(8) A ta m d gosl 9 1 9 137 1955

diet or with eggs Olive oil and ground nut oil did not raise the serum cholesterol levels

Changes in serum cholesterol level are due to some factor additional to the cholesterol content of the dietary fat One such factor is the type of fatty acid A possible common difference between animal fats and hydrogenated vegetable fat, on one hand and natural vegetable oils and marine oils on

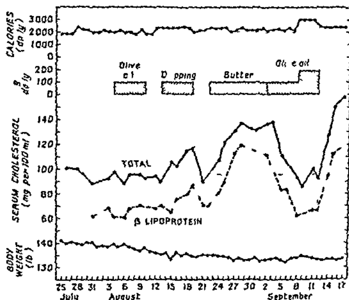


Fig 1 6—Chang n s um h leste l lev ls n on E r pean bject coincided with chang in m l fat nt ke On bas c l w f t and pr te d et w th no chol ster l ol ve oil d d not r se le el or ma nta n se when sub t t t d for butter E en when t pr ded 60% of total calorie s rum chole te l ros aga n onl when full d t of b ef a d eg t bl s (140 Gm fat) wa given M erum cholesterol lev l befo e fat fe d g w s 95 6±5 5 mg/100 ml (Court y of B ont St wart B et al Lancet 1 5 1526 Apr 1956)

the other is not the cholesterol sitosterol vitamin or protein content but is somehow connected with the proportion of highly unsaturated and saturated fatty acids in the fat Sunflower seed oil and a segregated highly unsaturated fatty acid fraction from pilchard oil consistently depressed serum cholesterol levels when fed alone with a supplement of cholesterol or with animal fat

Evidence that dietary fat influences development of coronary heart disease in man although strong is circumstantial and mainly derived from epidemiologic studies T re

ories provided by fats in the habitual diet of the population and is not related to cholesterol content of the diets More prosperous men usually less active physically tend to have higher cholesterol values than the rest of the community Ancel Keys Joseph T Anderson Mario Aresu Gunnar Biorck John F Brock B Bronte Stewart Flaminio Fidanza Margaret Haney Keys Haqvin Malmros Arrigo Poppi Teodoro Posteli Bengt Swahn and Alfonso del Vecchio[9] reaffirm their previous conclusions that diet not physical activity is characteristically responsible for differences in serum cholesterol

In men who worked as firemen policemen at light work or heavy manual labor serum cholesterol in the group was independent of the habitual physical activity but was correlated with diet When values for men in three activity levels in Cape Town from three socioeconomic levels were plotted (Fig 127) only among the Bantu was total cholesterol lower in those with heavy manual labor and re examination of the dietary history showed the proportion of fat in the diet decreased with increasing physical activity in this group

Differences in physical activity do not explain the large differences in serum cholesterol found when groups with different dietary habits are compared In some populations men doing heavy manual labor tend to have somewhat lower serum cholesterol values but their diets are found to be lower in fats also The composition of the diet generally tends to be so related to the habitual level of physical activity

The habitual diet especially its fat content has much more influence than physical activity on concentration of total cholesterol and β lipoprotein cholesterol in the blood serum

Treatment of Familial Hypercholesteremia with a Plant Sterol is reported in a brother and sister by Abner H Levkoff and K T Knode[1] (South Bend Ind) Sitosterol a plant sterol derived from soybeans cotton seed and corn is not absorbed from the intestinal tract and interferes with absorption of cholesterol presumably by combining with it to form a mixed crystal which does not pass the intestinal barrier

Boy and girl 11 and 10 were in good health Physical examination was normal Cholesterol in the blood was determined because

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(9) J Cl I st 5 1173 1181 Oct be 1956
(1) J diat 19 88 90 J ry 1957

terol in the serum increased as the percentage of calories obtained from fats increased in an almost straight line correlation. A positive correlation was also found between low blood pressures in the examined populations, serum cholesterol *and dietary fat intake*.

The low dietary fat consumption in these poor Bosnian villages results in low incidence of atherosclerosis.

Physical Activity and Diet in Populations Differing in Serum Cholesterol. The average concentration of cholesterol tends to be directly related to the proportion of the total cal

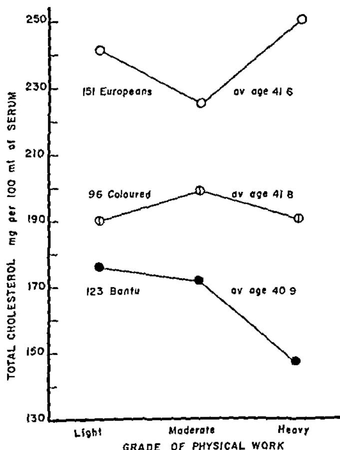


Fig. 127.—Mean serum total cholesterol values for men i Cape Town (aged 30 51) lass fi d ccord ng to phy cal acti ty demanded by thei h b tu l work. (Courte y of Keys A. et al J Clin. Inv t. 35 1173 1181 Oct ber 1956.)

other fat meal is ingested The usual patient must have no more than one fatty meal each 24 hours a fat free breakfast a fat free lunch and no restriction whatever on the evening meal If the patient prefers a heavy meal during the day the evening meal must be fat free

Patients on this regimen have responded well and have not modified their way of life drastically Several have been followed 4 7 years Most have broken the fat spacing at some time for one reason or another but control has easily been re established by a period of rigid fat restriction equal in time to fat binge followed by a return to the fat spaced pro gram In many the severity of angina pectoris has lessened or even disappeared and xanthoma secondary to hyperlipe mia has disappeared

Familial hyperlipemia responds to this regimen familial hypercholesteremia does not It therefore is necessary to dis tinguish between these two conditions if possible

► [The introduction of intravenous fat emulsions as a source of calories for patients who must maintain their nutrition on intravenous feedings has been slow and painful It finally appears that suitable preparations are available and that positive nitrogen balance can be obtained with these emul ions The incidence of reactions and of hemolysis previously serious bugbears appears to be negligible —Ed.]

Metabolic Effects of Fat Emulsions Administered Intrave nously to Human Subjects are described by William B A Bentley and Theodore B Van Itallie[3] (St Luke s Hosp New York) Four healthy volunteers were maintained on constant diets inadequate in calories but adequate in pro tein and subsequently given 15% fat emulsions intrave nously

Negative nitrogen and potassium balances were produced by the inadequate diets In 3 this negative balance was sig nificantly ameliorated when fat emulsions providing 1 200 1 400 calories were added intravenously In each the potas sium balances responded more dramatically than the nitro gen balances and the former became positive When fat was added to the basic diet orally in amounts equivalent to that provided intravenously the sparing effects on nitrogen and potassium balances were similar (Fig 128)

These studies constitute further evidence that suitably pre pared fat emulsions administered intravenously to human

(3) J Lab. & Cl M d 48 184-193 A gu t, 1956

2 maternal uncles and the mother died suddenly at ages 50 51 and 47 of occlusive vascular disease Serum levels were 354 and 338 mg/100 ml Phospholipid and total lipid levels were also elevated When sitosterol was given serum cholesterol levels were reduced to 260 and 290 mg/100 ml respectively No added reduction occurred when cholesterol was restricted in the diet and sitosterol continued Neither child lost weight during the study There were no objections to taking the sterol suspension and it was preferable to the low cholesterol diet

Whether reduction of concentration of cholesterol in the serum as here accomplished, can prevent atherosclerematous complications of familial hypercholesteremia is problematic However until the relation of cholesterol to atherosclerosis is further evaluated in this disease such therapy seems indicated

► [Interest in finding an antidote to a high fat intake has taken many forms The use of sitosterol was also reported by Farquhar Smith and Dempsey (Effect of beta sitosterol on serum lipids in young men with arteriosclerotic heart disease this YEAR BOOK p 393) and by Soche and Eston (A M A Arch. Int Med 97 738 1956) A number of other substances are also currently being investigated These include thyroid by Strisower *et al* (Lancet 1 120 Jan 9 1957) brain extract by Jones (J Lab & Clin Med 47 261, 1956) and nicotinic acid by Parsons *et al* (Proc. Staff Meet. Mayo Clin 31 377 June 27 1956) —Ed]

Spaced Fat Feeding Regimen of Management for Familial Hyperlipemia is advocated by Charles F Wilkinson Jr[2] (New York Univ) The metabolic defect in familial hyperlipemia is retarded removal of ingested fat from the blood stream after normal absorption and is usually the only abnormality found in the heterozygous state In the homozygous abnormal hepatosplenomegaly abdominal crises and secondary xanthoma may be found The mode of inheritance is that of an incomplete dominant such as essential familial hypercholesteremia Fat gradually accumulates in the blood stream in a series of steplike increments Elevated cholesterol is secondary and can be controlled if hyperlipemia can be

Existing hyperlipemia and secondary elevation of cholesterol and phospholipid can be reduced by rigid fat restriction for the time necessary to bring the blood lipids within the accepted normal limits These levels may be maintained by properly spacing ingested fat in time so that even with the slow removal rate, postprandial hyperlipemia will return to the fasting level now normal before an

(2) Ann Int. Med. 45 674-680 October 1956

protein free isocaloric diets containing the same amounts of carbohydrate or fat as before

Results indicated that fat can inhibit endogenous protein catabolism but apparently not to the same degree as carbo hydrate With carbohydrate diets nonprotein nitrogen ex cretion decreased 68% compared with that in rats that were not forced fed whereas diets containing Mazola oil oleic acid and glycerol decreased excretion by 53 50 and 63% respectively

The difference between these results and others showing no protein sparing effect from fat may be attributed to the pre experimental diets of the animals It is not surprising that fat like carbohydrate should spare nitrogen Protein carbohydrate and fat share a common final metabolic path way When there is a demand for energy carbohydrate is probably used preferentially to protein Fat also is used in preference to endogenous protein Since fat is not converted to carbohydrate protein must form the carbohydrate in the phlorhizinized animal Thus protein sparing is less effective in fat fed than in carbohydrate fed phlorhizinized animals

Effect of Intravenous Fat Emulsions on Total Bilirubin Output as Measure of Hemolysis in Human Subjects Most of the problems of stability and particle size of fat emulsions have been overcome but adverse reactions in human subjects remain common Fever is the most common Among 110 pa tients receiving 1 or more infusions John F Mueller Morton I Grossman and Hugo C Moeller[5] (Fitzsimons Army Hosp Denver) report that 34% developed rectal temperatures over 101 6 F and half of these had an associated chill

Free fatty acids are known to produce in vitro hemolysis and infusion of relatively soluble short chained glycerides have been reported to cause intravascular hemolysis and se vere reactions In experimental animals large amounts of fat given intravenously have increased the bilirubin Because of these findings it was postulated that the febrile reaction in human beings after infusion of fat is caused by intra vascular hemolysis

To test this hypothesis 600 cc of 15% fat emulsion was infused into 11 patients who had indwelling T tubes in the common duct Quantitative analysis of bile recovered from

(5) J Lab & Clin Med. 48 379 385 September 1956

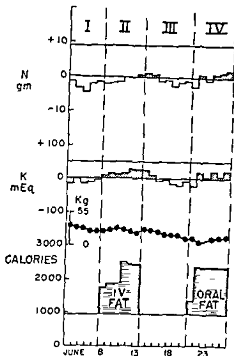


Fig 128 —Compa n of ffects f ntraveno sly admin ste ed f t a d supple me t ry f t g en o ally o nit og a d potas um b la ces respect ly b- je t cal cally d fici t d et (Court sy of B tl y W B A and V n Itall T B J Lab & Cl n Med. 48 184 193 Aug st 1956)

beings are utilized for calories and can decrease nitrogen and potassium deficits induced by diets inadequate in calories

► [Similar observations were reported by Levey *et al* (J Lab & Clin Med 49 61 1957) —Ed]

Nitrogen Sparing Action of Neutral Fat and Fatty Acids in the Phlorhizinized Rat Carbohydrate spares protein whether or not the animal is starving or is receiving a diet which does or does not contain protein However studies dealing with the ability of fat to prevent excessive nitrogen loss are conflicting To explore this problem further Clarence Cohn and Dorothy Joseph[4] (Michael Reese Hosp) forced fed rats a high carbohydrate or high fat diet for several weeks then injected phlorhizin and followed this with

(4) P oc Soc E per B l & Med. 93 462-466 Decembe 1956

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(5) J Lab & Cl M d 48 379 385 S ptembe 1956

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METABOLIC DISEASE

Concept of Secondary Gout, Relation to Purine Metabolism in Polycythemia and Myeloid Metaplasia is elucidated by Alexander B Gutman T F Yu and Bernard Weissmann[6] (New York) Gout seems to be a disorder of multiple pathogenesis Classic *primary* gout is a genetically determined error of metabolism in which biosynthesis of uric acid and other purines occurs by direct metabolic pathways not involving augmented nucleic acid formation and breakdown Other inborn errors of metabolism may be included in this classification

Secondary gout is an acquired complication particularly of hemopoietic disorders Incidental to much faster turnover of nucleic acids related to overproduction of blood cells there is excessive biosynthesis of uric acid and other purines by indirect metabolic pathways involving increased formation and degradation of nucleic acids The hemopoietic disorders include myeloid metaplasia polycythemia vera secondary polycythemia chronic myelocytic leukemia acute leukemias and chronic hemolytic anemias Hyperuricemia is common in these diseases but does not per se constitute secondary gout This diagnosis should be reserved for the few patients in whom clinically overt gout develops

Study of the rate and magnitude of glycine N^{15} incorporation in urinary uric acid show significant differences between patients with primary and secondary gout In normal persons and patients with primary gout there is rapid incorporation into urinary uric acid with a peak in 2 4 days The concentration in patients with primary gout is significantly higher In patients with secondary gout there is increase in urinary uric acid N^{15} until the 10th day with a gradual decline thereafter Rates of incorporation are the same in pa

(6) Tr A Am. Physicians 69 2 9 238 1956

tients with polycythemia and myeloid metaplasia whether or not gout is clinically present.

The protracted maximal glycine N^{15} incorporation into urinary uric acid in polycythemia vera and agnogenic myeloid metaplasia presumably reflects the rate of turnover of cellular nucleic acids concerned with hemopoiesis in these disorders Glycine is a precursor of the purine components of nucleic acids adenine and guanine which are ultimately excreted mostly as uric acid The time relations observed appear consistent with this interpretation

Observation on Gout—the Joint Warning Sign is described by T E Weiss and Albert Segaloff[7] (New Orleans) Gout is classically characterized by sudden onset of excruciating pain in the great toe followed in a few hours by swelling redness and exquisite tenderness Relief from acute symptoms is more rapid if colchicine is administered early in the attack

Polyuria nocturia anorexia irritability indigestion or even a sense of well being have been considered premonitory signs but are relatively rare However of 95 patients with recurrent attacks of gout 60 could detect a subjective reaction in the involved joint before the attack This was described as something they feel in the joint expressed as burning tingling stiffness numbness warmth or awareness as a mild but different type pain The intense pain characteristic of acute gout followed the warning sign reaching a peak in a few minutes to several hours Only patients who had experienced several acute attacks could identify a pattern of symptoms with an initial warning sign Those who had only 1 or 2 bouts seemed aware only of the acute intense discomfort

These sensations suggest that the phenomenon of acute gout arises before the acute pain begins Recognition of this pattern has proved of diagnostic and therapeutic value This joint warning sign appears characteristic of gout and rarely appears in rheumatoid arthritis At the first warning of gout prompt therapy should be initiated to abort or minimize an acute incapacitating attack Patients who have acute attacks of gout should be alert to such warning signs and start taking colchicine when they are recognized

► [Probenecid one of the mainstays of treatment of primary gout, is

(7) Am. Pract. & Digest Treat. 7 969 970 J 1956.

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(6) Tr A Am Physicians 69 2 9 238 1956

of acute attacks but the response has been variable and con clusions impossible because of spontaneous remissions

Chlorpromazine 25 mg 3-4 times daily by mouth in each case was followed promptly by disappearance of pain and nervous symptoms Paralyses which were already established were unaffected In 3 patients a single 100 mg dose was fol lowed by complete clinical remission In 1 of these the effect of chlorpromazine during a subsequent mild relapse of pain was relatively short Pain was promptly relieved but no significant change in porphyrin or porphobilinogen excre tion was noted during the study Possibly the drug interrupts a vicious cycle permitting spontaneous remission to occur

In 2 patients rauwolfia alkaloid was valuable as main tenance therapy Nervous symptoms were absent in both while taking the drug but recurred when it was withdrawn

Present experience indicates that chlorpromazine is rea sonably safe in cases of acute porphyria and does not pre cipitate relapses It is the most consistently effective remedy available for pain and nervous manifestations

► [A similarly encouraging report has been published by Monaco *et al* (New England J Med. 256 309 Feb 14 1957) Readers interested in this area will find Watson s review (Porphyrin metabolism in anemias A.M.A. Arch Int Med. 99 323 1957) of value —Ed]

Multiple Serum Protein Deficiencies in Congenital and Acquired Agammaglobulinemia Patients with severe re curring bacterial infections may have no serum gamma glob ulins This may occur as a physiologic or transient form in infants as a congenital form inherited as a sex linked reces sive in males or as an acquired form in both sexes with onset of infections in adolescence or adulthood Congenital and ac quired forms are due to absence of plasma cells in the tissues with consequent deficiency of gamma globulin and failure of antibody synthesis It has previously been shown that small amounts of gamma globulin are usually present less than 25 mg /100 ml in the congenital form and less than 100 mg /100 ml in the acquired form

David Gitlin Walter H Hitzig and Charles A Janeway[1] (Boston) by using rabbit and horse antiserums confirmed that the deficiency of gamma globulins in agammaglobuline mia is often incomplete In antigenic analysis of serums from 8 patients with congenital agammaglobulinemia 3 with

(1) J Cl I est. 35 1199 1204 Nov mber 1956.

notable for the scarcity of toxic reactions Au trian and Boger however have reported 1 case (A M A Arch Int Med. 98 505 1956) in which sensitization occurred after the drug had been interrupted Desensitization was possible by graded tiny doses —Ed]

Phenylketonuria Two Unusual Cases are reported by Niels L Low Marvin D Armstrong and John W Carlisle[8] (Univ of Utah) Phenylketonuria is an inherited biochemical abnormality in oxidation of phenylalanine to tyrosine *Most reports have emphasized the severe mental defect which accompanies the biochemical disorder However several cases have been reported with little or no mental retardation as in the 2 reported*

Previous emphasis on severe mental retardation was probably due to the fact that the patients studied had been detected by screening inmates of institutions and examining their siblings It is now evident that affected persons can easily escape detection Phenylketonuria is not incompatible with normal or near normal mental function This may be significant in future treatment of infants with phenylketonuria since it may not be necessary to continue the somewhat difficult dietary control of phenylalanine intake for more than a few years during early childhood

Normal or near normal intelligence in phenylketonuria could presumably exist under the following conditions (1) during the first few months of life because biochemical abnormalities seizure disorder and deterioration usually are not yet present (2) in children maintained on restricted phenylalanine intake before deterioration is evident and (3) in persons in whom oxidation of phenylalanine is incompletely blocked as perhaps in the authors 2 cases Excretion of phenylpyruvic acid and the serum level of phenylalanine in both patients were considerably lower than usual in phenylketonuria

Chlorpromazine in Treatment of Porphyria is reported in 9 cases by James C Melby John P Street and C J Watson[9] (Univ of Minnesota) *No agent has been found that will correct the metabolic defect of porphyria Certain ganglioplegics ACTH and hydrocortisone or its analogues have been thought in some cases to interfere with the progress*

(8) Lancet 917 918 Nov 3 1956
(9) J.A.M.A 16 174 178 Sept. 15 1956

The results were unequivocal The patient with idiopathic hypoproteinemia had a much increased albumin turnover Despite the greatly reduced amount of protein at her disposal she degraded and synthesized over twice the normal amount of albumin/kg body weight Increased renal excretion of iodine indicates that the albumin was not only removed but also broken down more quickly

Increased protein catabolism not reduced synthesis is the basic defect in this disease A better name would be hypercatabolic hypoproteinemia Plasma proteins appear selectively affected Hemoglobin turnover occurs at its usual rate and the rate of growth in children is unaffected

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MISCELLANEOUS

Absorption of Irrigating Solution and Associated Changes on Transurethral Electroresection of Prostate During transurethral electroresection of the prostate or at its close the patient may abruptly become hypertensive restless nauseated dyspneic and cyanotic and complain of blacking out N S R Maluf J S Boren and G E Brandes[3] (Houston) studied changes in weight serum sodium chloride and protein and cerebrospinal fluid pressure chloride and protein in 15 consecutive patients during this procedure The irrigating fluid was 1 2% glycine

During the procedure 14 gained weight 2 gaining over 4 kg during the resection period of 80 minutes both became hypertensive It appears that a patient who is a fair surgical risk who weighs about 60 kg preoperatively and who becomes apprehensive dyspneic and hypertensive during the procedure has absorbed over 3 5 kg irrigation fluid within about 1½ hours

Serum sodium level fell at the close of resection in all but 1 patient The fall was pronounced in the 2 who became hypertensive The actual serum sodium level immediately after resection is nearly always considerably higher than the theoretical value based on the assumption that water absorbed remains in the extracellular fluid The inference that some of the water absorbed becomes intracellular is corroborated by

(3) J U 1 75 824 836 M y 1956

the acquired form and 6 normal adults and by agar diffusion and electrophoresis at least two plasma proteins besides gamma globulin were demonstrated to be absent or deficient in this disease These proteins migrate as beta globulins in agar They apparently have no antigenic relation to gamma globulin

Other plasma proteins may be absent or deficient in this syndrome The number which could be studied depended on the number of antibodies present in the antiserums used

Idiopathic or Hypercatabolic Hypoproteinemia Case Examined by I^{131} Labeled Albumin. Hypoproteinemia is not uncommon but is usually caused by external loss of protein in the urine through the skin by bleeding or because of reduced protein synthesis A few reported cases have remained unexplained and labeled idiopathic Michael Schwartz and Bagger Thomsen[2] proved that 1 patient had hypoproteinemia because of rapid turnover of albumin

The main sign of this disease is edema which varies with hypoproteinemia Albumin and globulin are equally affected Oral administration of protein in large amounts does not affect the serum protein level although a highly positive nitrogen balance can be induced

Woman 25 was hospitalized for edema of the legs present since age 17 and recently involving the left hand She had never had facial edema Improvement was slight on bed rest The only abnormality in extensive laboratory tests was marked decrease in serum protein levels affecting all fractions equally High protein diet testosterone and ACTH were ineffective

To determine the rate of turnover I^{131} labeled human serum albumin was administered to the patient and to 3 normal subjects All 4 were hospitalized given ordinary diet and permitted moderate activity To secure rapid excretion of iodine and inhibit thyroid uptake of I^{131} KI was also given The labeled albumin was given intravenously 30 mg albumin with radioactivity equal to about 90 μc In the normal subjects serum levels of protein ranged from 6 8 to 7 4 Gm /100 ml of albumin 4 5 to 5 5 Gm /100 ml and of total exchangeable albumin 308-440 Gm Corresponding figures in the patient were 4 3 3 and 190 The albumin turnover half time (T/2) in the normal subjects was 21 3 23 9 days in the patient 7 2 days Albumin degradation in percentage day was 2 9 3.26% in the normals 9 64% in the patient an average of 0 17 Gm /day/kg in the normals compared with 0 37 Gm /day/kg in the patient Total renal excretion of I^{131} in the first 14 days following an injection was 50% in 1 normal subject compared with 92% in the patient

(2) Brit M J 1 14 17 Jan 5 1957

mothers of the patients in 3 of the 4 families drank about 6 pints of fluid a day even in winter Of the 6 tested 4 had to drink water during the night when they were children but less commonly as adults In the fourth family the mother s sister but not the mother or grandmother had polydipsia during childhood Pregnancy had no special effect

The mean urine specific gravity after overnight dehydra tion in the mothers was 1 011 of the grandmothers 1 013 and among other female relatives 1 016 The mothers and grand mothers thus formed a specific group with concentrating ability significantly lower than in controls Other female rel atives had a lower mean specific gravity than controls and higher than the mothers but differences were not statisti cally significant Although there is some overlap a mean spe cific gravity of 1 018 on 3 morning specimens of urine after overnight dehydration differentiates most heterozygote car riers from women who are not carriers of the gene Diagnosis based on this urine concentration test agrees well with the genetic analysis of the 4 pedigrees The vasopressin concen tration test was of no diagnostic aid in differentiating hetero zygote carriers from normal controls

Experimental Study of Magnesium Deficiency in Man is reported by M G Fitzgerald and Paul Fourman[5] (Royal Infirm Cardiff Wales) The total amount of magnesium in an adult man is about 2 000 mEq In diabetic ketosis losses of magnesium have been estimated to be 50 70 mEq which in comparison do not appear large Some authors recom mend the addition of magnesium to parenteral fluids when deficits are suspected but the importance and physiologic significance of these deficits have not been assessed In grow ing animals lack of magnesium is lethal

Diets containing little magnesium but adequate in cal ories and protein were given to 2 normal men who also re ceived an ion exchange resin orally which removed magne sium from the body Magnesium balance studies were made Both men withstood the experiments well and pursued ordi nary duties but claimed weakness during the depletion No changes attributable to a magnesium deficiency were seen in blood pressure pulse rate ECG BMR or maximal con centration of urine

(5) Cl S 15 635-647 No mbc 1956

identical changes in serum chloride levels During the latter half of the day of surgery the serum sodium level begins to return to normal In most patients this is due to diuresis and is correlated with simultaneous fall in weight Concentrated (5%) sodium chloride effectively promotes diuresis and relieves the symptoms of hypervolemia

Cerebrospinal fluid pressure tended to rise during resection averaging an increase of 79 mm fluid The greatest rise occurred in the patient who showed the largest weight gain and became hypertensive The chloride concentration in the cerebrospinal fluid typically fell but was not significant

The hydrostatic pressure with which the irrigating fluid was introduced was a significant factor All but 2 resections were performed with irrigation pressures of 115 135 cm water The other 2 patients were operated on with pressures of 85 105 cm water and gained only 0 1 1 1 kg fluid

The amount of fluid absorbed during transurethral electroresection of the prostate depends on the hydrostatic pressure of the irrigating fluid extent of resection (exposure of intraprostatic venous channels) and duration of exposure

► [This dangerous syndrome has not previously received the attention it deserves In cases where acute tubular necrosis has followed transurethral resection the usual diagnosis has been hemolysis with hemoglobinuria nephrosis Although hemolysis may play some part when distilled water is used as irrigating solution water intoxication is probably a more important source of difficulty Since excessive absorption of water can be prevented by reducing the irrigating pressure this complication may soon cease to worry us —*Ed*]

Carrier State in Nephrogenic Diabetes Insipidus Sex linked nephrogenic diabetes insipidus is characterized by polyuria from infancy and is resistant to vasopressin Renal function is otherwise normal It is important to detect women heterozygous for this condition to reduce the number of affected males and to begin treatment early in life Early diagnosis is essential because patients die early or show severe mental retardation if they are not kept fully hydrated Cedric Carter and Michael Simpkiss[4] (Hosp for Sick Children London) took histories did overnight urine and vasopressin concentration tests in mothers and maternal grandmothers of 4 boys with nephrogenic diabetes insipidus Results were compared with those in controls

Histories revealed that the mothers and maternal grand

(4) Lancet 2 1069 1073 Nov 24 1956

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The magnesium lost from the body was 42 mEq and 72 mEq in the 2 men Though blood levels of magnesium apparently did not fall and no other notable effects of the deficiency were found it was associated with transit loss of potassium gain of sodium and chloride and presumably increase in volume of extracellular fluid

The experiments were terminated by intravenous injection of magnesium Of 45 and 89 mEq injected 25 and 45% were retained No magnesium was retained in 2 comparable control experiments in which magnesium had been provided throughout In the depletion but not in the control experiments injections were associated with loss of sodium and chloride

The compartment of the body or the tissue which sustained the losses is unknown The total magnesium in the extracellular fluid and the concentration of magnesium did not fall In rats, the concentration in the intracellular fluid does not fall during deficiency and this may also be true in man Bone contains half the magnesium in the body and in rats provides magnesium when growing rats are depleted of the ion Perhaps this occurs in clinical deficiency in man The mechanism of deposition and uptake of magnesium at the surface of bone crystal is not known nor is the mechanism of kidney control in conservation of the ion

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